Package leaflet: Information for the patient

PREMARIN® 0.625 mg
Prolonged-release Tablets

PREMARIN® 1.25 mg
Prolonged-release Tablets

(conjugated oestrogens)

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Premarin is and what it is used for

Premarin is a Hormone Replacement Therapy (HRT). It contains the female hormone oestrogen. Premarin is used to treat some of the symptoms and conditions associated with the menopause.
Premarin is usually prescribed for women who have had their womb removed (hysterectomy). However women who have not had this operation can still take Premarin and their doctor may prescribe a second type of tablet containing another hormone called a progestogen to be taken 12-14 days per month as well as the Premarin tablets.

Premarin is used for:

Relief of symptoms occurring after menopause
During the menopause, the amount of the oestrogen produced by a woman's body drops. This can cause symptoms such as hot face, neck and chest ("hot flushes"). Premarin alleviates these symptoms after menopause. You will only be prescribed Premarin if your symptoms seriously hinder your daily life.

Prevention of osteoporosis
After the menopause some women may be at risk of developing fragile bones (osteoporosis). You should discuss all available treatment options with your doctor.
If you are at an increased risk of fractures due to osteoporosis and other medicines are not suitable for you, you can use Premarin 0.625 mg or 1.25 mg Prolonged-release Tablets to prevent osteoporosis after menopause.

You must talk to a doctor if you do not feel better or if you feel worse after taking this medicine.

2. What you need to know before you take Premarin

Medical history and regular check-ups

The use of HRT carries risks which need to be considered when deciding whether to start taking it, or whether to carry on taking it.

The experience in treating women with a premature menopause (due to ovarian failure or surgery) is limited. If you have a premature menopause the risks of using HRT may be different. Please talk to your doctor.

Before you start (or restart) HRT, your doctor will ask about your own and your family's medical history. Your doctor may decide to perform a physical examination. This may include an examination of your breasts and/or an internal examination, if necessary.

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

Go for regular breast screening, as recommended by your doctor.

Do not take Premarin
If any of the following applies to you or you are not sure **talk to your doctor** before taking Premarin.

Do not take Premarin:

- If you are **allergic** to **conjugated oestrogens** or any of the other ingredients of this medicine (listed in section 6).
- If you have or have ever had **breast cancer**, or if you are suspected of having it.
- If you have **cancer which is sensitive to oestrogens**, such as cancer of the womb lining (endometrium) or if you are suspected of having it.
- If you have any **unexplained vaginal bleeding**.
- If you have **excessive thickening of the womb lining** (endometrial hyperplasia) that is not being treated.
- If you have or have ever had a **blood clot in a vein** (thrombosis) such as in the legs (deep vein thrombosis) or the lungs (pulmonary embolism).
- If you have a **blood clotting disorder** (such as protein C, protein S or antithrombin deficiency).
- If you have or recently have had a disease caused by blood clots in the arteries, such as a **heart attack, stroke** or **angina.**
- If you have or have ever had a **liver disease** and your liver function tests have not returned to normal.
- If you have a rare blood problem called "porphyria" which is passed down in families (inherited).
- If you know or suspect you are pregnant, or you are breast-feeding.

If any of the above conditions appear for the first time while taking Premarin, stop taking it at once and consult your doctor immediately.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Premarin if you have ever had any of the following problems, before you start the treatment, as these may return or become worse during treatment with Premarin. If so, you should see your doctor more often for check-ups:

- fibroids inside your womb
- growth of womb lining outside your womb (endometriosis) or a history of excessive growth of the womb lining (endometrial hyperplasia)
- increased risk of developing blood clots (see section 2 'Blood clots in a vein (thrombosis)' for more detail)
- increased risk of getting a oestrogen-sensitive cancer (such as having a mother, sister or grandmother who has had breast cancer)
- high blood pressure

- a liver disorder, such as a benign liver tumour
- diabetes
- gall bladder disease or gallstones
- migraine or severe headaches
- a disease of the immune system that affects many organs of the body (systemic lupus erythematosus, SLE)
- epilepsy
- asthma
- a disease affecting the eardrum and hearing (otosclerosis)
- a very high level of fat in your blood (triglycerides)
- fluid retention due to cardiac or kidney problems
- hypocalcaemia (low calcium levels)
- thyroid deficiency.

Stop taking Premarin and see a doctor immediately
If you notice any of the following when taking HRT:

- any of the conditions mentioned in the "Do not take Premarin" section
- yellowing of your skin or the whites of your eyes (jaundice). These may be signs of a liver disease
- a large rise in your blood pressure (symptoms may be headache, tiredness, dizziness)
- migraine-like headaches which happen for the first time
- if you become pregnant
- have an allergic reaction, signs of which include a rash, itching, shortness of breath, difficulty in breathing and a swollen face
- if you notice signs of a blood clot, such as:
    - painful swelling and redness of the legs
    - sudden chest pain
    - difficulty in breathing

  For more information, see section 2 "Blood Clots in a vein (thrombosis)" below.

Note: Premarin is not a contraceptive. If it is less than 12 months since your last menstrual period or you are under 50 years old, you may still need to use additional contraception to prevent pregnancy. Speak to your doctor for advice.

HRT and cancer

Excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the lining of the womb (endometrial cancer)

Taking oestrogen-only HRT will increase the risk of excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the womb lining (endometrial cancer).

Taking a progestogen in addition to the oestrogen for at least 12 days of each 28 day cycle protects you from this extra risk. So your doctor will prescribe a progestogen separately if you still have your womb. If you have had your womb removed (a hysterectomy), discuss with your doctor whether you can safely take this product without a progestogen.

In women who still have a womb and who are not taking HRT, on average, 5 in 1000 will be diagnosed with endometrial cancer between the ages of 50 and 65.
For women aged 50 to 65 who still have a womb and who take oestrogen-only HRT, between 10 and 60 women in 1000 will be diagnosed with endometrial cancer (i.e. between 5 and 55 extra cases), depending on the dose and for how long it is taken.

Premarin 0.625 mg and 1.25 mg prolonged-release tablets contain a higher dose of oestrogens than other oestrogen-only HRT products. The risk of endometrium cancer when using Premarin 0.625 mg and 1.25 mg prolonged-release tablets together with a progestogen is not known.

If you still have your womb, your doctor may prescribe a progestogen as well as oestrogen. If so, these may be prescribed separately, or as a combined HRT product.

If you have had your womb removed (a hysterectomy), your doctor will discuss with you whether you can safely take oestrogen without a progestogen.

If you've had your womb removed because of endometriosis, any endometrium left in your body may be at risk. So your doctor may prescribe HRT that includes a progestogen as well as an oestrogen.

Your product, Premarin, is an oestrogen-only product.

Irregular bleeding
You may have irregular bleeding or drops of blood (spotting) during the first 3-6 months of taking Premarin. However if the irregular bleeding:

- carries on for more than the first 6 months
- starts after you have been taking Premarin for more than 6 months
- carries on after you have stopped taking Premarin

➢ **see your doctor as soon as possible.**

Breast Cancer
Women who have breast cancer, or have had breast cancer in the past, should not take HRT.

Evidence shows that taking combined oestrogen-progestogen or oestrogen-only hormone replacement therapy (HRT) increases the risk of breast cancer. The extra risk depends on how long you use HRT. The additional risk becomes clear within 3 years of use. After stopping HRT the extra risk will decrease with time, but the risk may persist for 10 years or more if you have used HRT for more than 5 years.

Your risk of breast cancer is also higher:

- if you have a close relative (mother, sister or grandmother) who has had breast cancer
- if you are seriously overweight.

Compare
Women aged 50 to 54 who are not taking HRT, on average, 13 to 17 in 1000 will be diagnosed with breast cancer over a 5-year period.
For women aged 50 who start taking oestrogen-only HRT for 5 years, there will be 16-17 cases in 1000 users (i.e. an extra 0 to 3 cases).
For women aged 50 who start taking oestrogen-progestogen HRT for 5 years, there will be 21 cases in 1000 users (i.e. an extra 4 to 8 cases).

Women aged 50 to 59 who are not taking HRT, on average, 27 in 1000 will be diagnosed with breast cancer over a 10-year period.
For women aged 50 who start taking oestrogen-only HRT for 10 years, there will be 34 cases in 1000 users (i.e. an extra 7 cases).
For women aged 50 who start taking oestrogen-progestogen HRT for 10 years, there will be 48 cases in 1000 users (i.e. an extra 21 cases).

Regularly check your breasts. See your doctor if you notice any changes such as:

- dimpling of the skin
- changes in the nipple
- any lumps you can see or feel.

Ovarian Cancer
Ovarian cancer (cancer of the ovaries) is rare - much rarer than breast cancer, but it is serious. It can be difficult to diagnose, because there are often no obvious signs of the disease.

The use of oestrogen-only or combined oestrogen-progestogen HRT has been associated with a slightly increased risk of ovarian cancer.

The risk of ovarian cancer varies with age. For example, in women aged 50 to 54 who are not taking HRT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period. For women who have been taking HRT for 5 years, there will be about 3 cases per 2000 users (i.e. about 1 extra case).

Effect of HRT on heart and circulation

Blood Clots in a vein (thrombosis)
The risk of **blood clots in the veins** (also called **deep vein thrombosis**, or **DVT**), is about 1.3 to 3-times higher in HRT users than in non-users, especially during the first year of taking it.

Blood clots can be serious, and if one travels to the lungs, it can cause chest pain, breathlessness, fainting or even death. This condition is called pulmonary embolism, or PE.

DVT and PE are examples of a condition called **venous thromboembolism**, or **VTE**.

You are more likely to get a blood clot in your veins as you get older and if any of the following applies to you. Inform your doctor if any of these situations applies to you:
- you are unable to walk for a long time because of major surgery, injury or illness (see also section 3, If you need to have surgery)
- you are seriously overweight (BMI>30 kg/m^2)
- you have any blood clotting problem that needs long-term treatment with a medicine used to treat blood clots
- if any of your close relatives has ever had a blood clot in the leg, lung or another organ
- you have any blood clotting problem that needs treatment with a medicine used to prevent blood clots
- you have systemic lupus erythematosus (SLE)
- you have cancer
- you are pregnant or have recently had a baby.

For signs of a blood clot, see section 2“Stop taking Premarin and see a doctor immediately”.

Compare
Looking at women in their 50s who are not taking HRT, on average, over a 5-year period, 4 to 7 in 1000 would be expected to get a blood clot in a vein.
For women in their 50s who have been taking oestrogen-progestogen HRT for over 5 years, there will be 9 to 12 cases in 1000 users (i.e. an extra 5 cases).
For women in their 50s who have had their womb removed and have been taking oestrogen-only HRT for over 5 years, there will be 5 to 8 cases in 1000 users (i.e. 1 extra case).

If you’re going to have surgery, make sure your doctor knows about it or tell the surgeon that you are taking Premarin. You may need to stop taking Premarin about 4 to 6 weeks before the operation, to reduce the risk of a blood clot. Your doctor will tell you when you can start taking Premarin again.

Heart Disease (heart attack)
HRT is not recommended for women who have heart disease, or have had heart disease recently. If you have ever had heart disease, talk to your doctor to see if you should be taking HRT.

There is no evidence that HRT will prevent a heart attack.

Women over the age of 60 who use oestrogen-progestogen HRT are slightly more likely to develop heart disease than those not taking any HRT.

For women who have had their womb removed and are taking oestrogen-only therapy there is no increased risk of developing a heart disease.

If you get:
- a pain in your chest that spreads to your arm or neck
- **See a doctor as soon as possible and do not take any more HRT** until your doctor says you can. This pain could be a sign of heart disease.

Stroke
The risk of getting stroke is about 1.5 times higher in HRT users than in non-users. The number of extra cases of stroke due to use of HRT will increase with age. More recent analysis of risk in women aged 50 to 59 years suggests no increased risk for women taking 0.625 mg Premarin tablets.

Other things that can increase the risk of stroke include:
- getting older
- high blood pressure
- smoking
- drinking too much alcohol
- an irregular heartbeat.

If you are worried about any of these things, or **if you have had a stroke in the past**, talk to your doctor to see if you should take HRT.

Compare
Looking at women in their 50s who are not taking HRT, on average, 8 in 1000 would be expected to have a stroke over a 5-year period. For women in their 50s who are taking HRT, there will be 11 cases in 1000 users, over 5 years (i.e. an extra 3 cases).

If you get:
- unexplained migraine-type headaches, with or without disturbed vision
- **See a doctor as soon as possible and do not take any more HRT** until your doctor says you can. These headaches may be an early warning sign of a stroke.

Other conditions
HRT will not prevent memory loss. There is some evidence of a higher risk of memory loss in women who start using HRT after the age of 65. Speak to your doctor for advice.

Women with pre-existing hypertriglyceridemia (high levels of fat in the blood) may experience large increases of their plasma triglycerides, which can lead to inflammation of the pancreas (pancreatitis). If you have this condition your doctor will monitor you closely.

Other medicines and Premarin
Some medicines may interfere with the effect of Premarin. This might lead to irregular bleeding. Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription, herbal remedies or other natural products. Your doctor will advise you.

- Medicines for **epilepsy** (such as phenobarbital, phenytoin, carbamazepine).
- Medicines for **tuberculosis** (such as rifampicin, rifabutin).
- Medicines for **HIV infection** (such as nevirapine, efavirenz, ritonavir, nelfinavir).
- Other antibiotics or antifungal medicines (e.g. erythromycin, clarithromycin, ketoconazole, itraconazole).
- Herbal remedies containing **St. John's wort** (*Hypericum perforatum*).

- Metyrapone (most commonly used in the treatment of Cushing's syndrome).
- Cimetidine (used to treat stomach ulcers and reduce stomach acid).
- Dexamethasone (a corticosteroid).

HRT can affect the way some other medicines work:
- A medicine for epilepsy (lamotrigine), as this could increase frequency of seizures.

The way that Premarin works may be altered if other medicines are used at the same time.

Premarin with food and drink and alcohol
Drinking grapefruit juice may affect the way that your medicine works.

Laboratory tests
If you need a blood test, tell your doctor or the laboratory staff that you are taking Premarin, because this medicine can affect the results of some tests.

Pregnancy, breast-feeding and fertility
Premarin is for use in postmenopausal women only.
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
There is no evidence to suggest that taking Premarin will affect your ability to drive or to operate machinery.

Premarin contains lactose monohydrate, sucrose and may contain the colouring agent E110 (sunset yellow)
Lactose monohydrate and sucrose are sugars. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

The colouring agent E 110, which is present in the yellow tablet (1.25 mg) may cause allergic reactions.

3. How to take Premarin

Instructions for proper use
Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

If you have had a hysterectomy you are not expected to have a period. However, if you have not had a hysterectomy, you may be taking an additional progestogen tablet for 12-14 days each month, and you will probably have a "period", or withdrawal bleed each month at about the time you finish the additional progestogen tablets. This is caused by the hormones in the HRT and is perfectly natural. Some women taking "combined HRT" (oestrogen plus the additional progestogen) may experience a gradual reduction in withdrawal bleeding and it may eventually stop; this is quite normal. If you have heavy or irregular bleeding you should tell your doctor.

Do not to try to take off the coating or crush the tablets, as this could affect the way Premarin works.

Dosage
Your doctor will aim to prescribe the lowest dose to treat your symptom for as short as necessary. Speak to your doctor if you think this dose is too strong or not strong enough.

The recommended dose is one tablet per day (0.625 mg or 1.25 mg), to be swallowed with a drink of water.

You may start your first pack at any convenient time. However, for women with a uterus if you are transferring from a sequential HRT product (an HRT product that gives you a monthly bleed), treatment

should begin the day following completion of the prior product unless instructed otherwise by your doctor.

Do not leave a break between packs unless your doctor tells you to. Do not stop taking Premarin without first discussing it with your doctor.

Use in children and adolescents
Safety and effectiveness in paediatric patients have not been established.

Duration of treatment
That really depends on why you and your doctor have decided on a course of treatment. If you are taking HRT to relieve your immediate menopausal symptoms like hot flushes and night sweats, you may be prescribed HRT for a relatively short period of time.

If, however, you or your doctor are worried about osteoporosis you may be prescribed HRT for longer.

If you take more Premarin than you should
If you take too many tablets do not worry, Premarin contains natural hormones and it is unlikely that serious problems will occur. If in any doubt consult your doctor or pharmacist.

You may feel some nausea (sickness), or experience a short period of vaginal bleeding (unless you have had a hysterectomy) if you take too many tablets.

If you forget to take Premarin
If you forget to take a dose, take it as soon as you remember, then go on as before. If more than one tablet has been missed take the tablet for the day that you remember and continue as normal. Do not take a double dose to make up for a forgotten tablet. Missed pills may cause breakthrough bleeding in women with a uterus (womb).

If you need to have surgery
If you are going to have surgery, make sure your doctor and/or your surgeon knows that you are taking Premarin. You may need to stop taking Premarin about 4 to 6 weeks before the operation, to reduce the risk of a blood clot (see section 2 - "Blood Clots in a vein (thrombosis)". Ask your doctor when you can start taking Premarin again.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist, or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following diseases are reported more often in women using HRT compared to women not using HRT:

- breast cancer
- abnormal growth or cancer of the lining of the womb (endometrial hyperplasia or cancer)
- ovarian cancer
- blood clots in the veins of the legs or lungs (venous thromboembolism)
- heart disease
- stroke
- probable memory loss (dementia) if HRT is started over the age of 65

For more information about these side effects, see section 2.
In addition to those discussed in section 2, the following side effects have been reported in women taking HRT:

Common: may affect up to 1 in 10 women

- breakthrough bleeding or spotting, vaginal inflammation
- breast tenderness, swollen breasts, nipple discharge, breast pain
- depression
- hair loss
- muscle and joint aches, leg cramps
- weight change (increase or decrease)
- changes in your triglyceride levels (fatty substances in the blood)

Uncommon: may affect up to 1 in 100 women

- changes in menstrual flow, inflammation of the vagina resulting in discharge
- thrush
- nausea, bloating, abdominal pain
- headache, migraine
- dizziness
- changes in mood including nervousness/anxiety
- changes in your interest in sex (increased or decreased libido)
- memory loss (dementia)
- visible swelling of the face or ankles
- itchiness, acne
- minor eye changes which may cause difficulties if you wear contact lenses
- gall bladder disease (e.g. gallstones)
- abnormal turning out of the cervix
- change in cervical mucus
- increase in hair growth
- discoloration of the skin especially of the face or neck known as "pregnancy patches" (chloasma)

Rare: may affect up to 1 in 1,000 women

- vomiting
- changes in breast tissue, milky secretion from the breasts
- allergic-like reactions
- irritability
- a worsening of glucose tolerance
- a worsening of asthma
- increase the growth of existing benign meningioma (a tumour of the membranes around the brain or spinal cord)
- inflammation of the pancreas
- inflammation of the colon (part of the intestine) which may present as lower left sided abdominal pain and/or bloody diarrhoea
- inflammation of veins just under the skin
- worsening of epilepsy
- heart attack
- increased size of fibroids
- dysmenorrhoea (lower back or abdominal pain during menstruation)

Very rare: may affect up to 1 in 10,000 women

- jaundice (e.g. yellowing of the skin)
- a worsening of chorea (an existing neurological disorder characterised by involuntary spasmodic movements of the body)

- a worsening of hypocalcaemia (low blood levels of calcium) in patients who already have a known risk of low levels of calcium in their blood
- enlargement of liver tumours
- worsening of porphyria (a rare inherited metabolic disorder)
- blood clots in the veins of the eye
- thickening of the lining of the uterus
- increase in blood pressure
- painful reddish skin nodules (erythema nodosum)
- rash with target-shaped reddening or sores (erythema multiforme)

These side effects are usually temporary and should get better over time.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance Website: www.hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Premarin

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

Do not store above 25ºC.

Do not use this medicine if you notice the pack has been opened or damaged.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Premarin contains

- The active substance is conjugated oestrogens. The tablets marked with "0.625" contain 0.625 mg conjugated oestrogens. The tablets marked with "1.25" contain 1.25 mg conjugated oestrogens.

- The other ingredients are lactose monohydrate, microcrystalline cellulose, magnesium stearate, hypromellose, sucrose, hydroxypropyl cellulose and polyethylene glycol. The coating on the maroon tablets contains hypromellose, titanium dioxide (E171), red aluminium lake (E129), macrogol and blue aluminium lake (E132). The coating on the yellow tablets contains hypromellose, titanium dioxide (E171), quinoline yellow aluminium lake (E104), Macrogol, polysorbate and sunset yellow (E110) (See section 2 Premarin contains lactose monohydrate, sucrose and the colouring agent E110 (sunset yellow)).

  The polish on the maroon and yellow tablets contains hypromellose and carnauba wax.

  The edible white ink on the maroon tablets contains titanium dioxide (E171), propylene glycol, and hypromellose. The edible black ink on the yellow tablets contains iron oxide black, propylene glycol, and hypromellose.

What Premarin looks like and contents of the pack
Premarin are prolonged-release tablets available in two different strengths.

Oval shaped, maroon tablets marked with “0.625” in white ink and oval shaped, yellow tablets marked with “1.25” in black ink.

Your tablets are supplied in a carton containing 28 tablets of the same colour.

Not all packs sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

The Marketing Authorisation Holder is:
Pfizer Healthcare Ireland Unlimited Company
The Watermarque Building
Ringsend Road,
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The Manufacturer is:
Pfizer Ireland Pharmaceuticals Unlimited Company
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