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Package Leaflet: Information for the user

Conjugated Estrogens Tablets U.S.P.

0.3 mg and 0.625 mg Tablets

Premarin¹®

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- If you have any further questions, ask your doctor.
- 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. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Premarin (Conjugated Estrogens) tablet is and what it is used for
2. What you need to know before you take Premarin (Conjugated Estrogens) tablet
3. How to take Premarin (Conjugated Estrogens) tablet
4. Possible side effects
5. How to store Premarin (Conjugated Estrogens) tablet
6. Contents of the pack and other information

1. What Premarin (Conjugated Estrogens) tablet is and what it is used for

What Premarin (Conjugated Estrogens) tablet is

Conjugated estrogens is an estrogen only Hormone Replacement Therapy (HRT) for oral use.

What Premarin (Conjugated Estrogens) tablet is used for

- Treatment of moderate to severe vasomotor symptoms associated with the menopause.

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- Treatment of vulvar and vaginal atrophy. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
- Prevention and management of post-menopausal osteoporosis. Prevention and management of post-menopausal osteoporosis in women at risk of future fractures. Therapy should start as soon as possible after the onset of menopause.
- Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.

2. What you need to know before you take Premarin (Conjugated Estrogens) tablet

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 tablet 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 tablet.

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

If any of the following applies to you or you are not sure, talk to your doctor before taking Premarin tablet.

Do not take Premarin (Conjugated Estrogens) tablet

- If you are **allergic** to **conjugated estrogens** 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 estrogens**, 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 tablet, stop taking it at once and consult your doctor immediately.

Warnings and precautions

Tell your doctor before taking Premarin tablet if you have ever had any of the following problems, as these may return or become worse during treatment with Premarin tablet. 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 “Blood clots in a vein (thrombosis)” for more detail)
- Increased risk of getting an estrogen-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 tumor
- Diabetes
- Gallbladder 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 (Conjugated Estrogens) tablet 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

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 estrogen-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 estrogen 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 estrogen-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.

If you still have your womb, your doctor may prescribe a progestogen as well as estrogen. 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 estrogen without a progestogen.

If you have 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 estrogen.

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

Irregular bleeding

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

- Carries on for more than the first 6 months
- Starts after you have been taking Premarin tablet for more than 6 months
- Carries on after you have stopped taking Premarin tablet
- 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 estrogen-progestogen or estrogen-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 estrogen-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 estrogen-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 estrogen-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 estrogen-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 estrogen-only or combined estrogen-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/m²)
- 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 estrogen-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 estrogen-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 tablet. You may need to stop taking Premarin tablet 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 tablet 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 estrogen-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 estrogen-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.

Ischaemic 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 (Conjugated Estrogens) tablet

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.

- 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 tablet works may be altered if other medicines are used at the same time.

Premarin (Conjugated Estrogens) tablet 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 tablet, because this medicine can affect the results of some tests.

Pregnancy and breast-feeding

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 tablet will affect your ability to drive or to operate machinery.

3. How to take Premarin (Conjugated Estrogens) tablet

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" (estrogen 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 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.

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 tablet 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 (Conjugated Estrogens) tablets 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 (Conjugated Estrogens) tablet

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 tablet. You may need to stop taking Premarin tablet about 4 to 6 weeks before the operation, to reduce the risk of a blood clot. Ask your doctor when you can start taking Premarin tablet 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
- 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
- breast cancer
- 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 tumor 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. If you get any side effects, talk to your doctor or pharmacist. This includes any side effects not listed in this leaflet.

5. How to store Premarin (Conjugated Estrogens) tablets

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

Store below 30°C.

6. Contents of the pack and other information

What Premarin (Conjugated Estrogens) tablet contains

Each tablet contains 0.3 mg or 0.625 mg of conjugated estrogens U.S.P.

List of Excipients

Conjugated Estrogens 0.3 mg Tablets:

Lactose Monohydrate (Spray Dried); Microcrystalline Cellulose; Hypromellose 2208, K100M (100,000 cps); Magnesium Stearate; Purified Water; Sucrose; Hydroxypropyl Cellulose; Hypromellose, 2910, E6 (6 cps); Hypromellose, 2910, E15 (15 cps); Polyethylene Glycol 400; Carnauba Wax

Colour:

Opadry®, Green, 15B21511 contains: HPMC 2910/Hypromellose, 3 cP, HPMC 2910/Hypromellose 2910, 6 cP, Quinoline Yellow Aluminium Lake (E104.), Macrogol/PEG 400, FD&C Blue #2/Indigo Carmine Aluminium Lake (E132), Titanium Dioxide, Polysorbate 80.

Opacode® WB NS-78-18011, white branding ink: Purified Water, Titanium Dioxide, Isopropyl Alcohol, Propylene Glycol, and Hypromellose 2910, 3 cP. Approximately 0.2 mg trace solids.

Conjugated Estrogens 0.625 mg Tablets:

Lactose Hydrate; Microcrystalline Cellulose; Hypromellose , 2910, E6 (6cps); Magnesium Stearate; Purified Water; White Soft Sugar; Hydroxypropyl Cellulose; Hypromellose ,2910, E6 (6cps); Hypromellose , 2910, E15 (15cps); Polyethylene Glycol 400; Carnauba Wax

Colour:

Opadry®, Maroon, 03B16083 contains: HPMC 2910/ Hypromellose, 6 cP, Titanium Dioxide, FD&C Red # 40/Allura Red Aluminum Lake (E129), PEG 400/ Macrogol, and FD&C Blue #2/Indigo Carmine Aluminum Lake (E132).

Opacode® WB NS-78-18011, white branding ink contains: Purified Water, Titanium Dioxide, Isopropyl Alcohol, Propylene Glycol, and Hypromellose 2910, 3 cP. Approximately 0.2 mg trace solids.

Contents of the pack

One blister pack of 28 tablets per carton.

All strengths/presentations mentioned in this document might not be available in the market.

Manufactured By:

M/s. Pfizer Ireland Pharmaceuticals, Little Connell, Co. Kildare, Newbridge, Ireland.

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