

Package leaflet: Information for the patient

PREMIQUE® Low Dose 0.3 mg/1.5 mg Modified Release Tablets conjugated estrogens and medroxyprogesterone acetate

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

What is in this leaflet

1. What Premique Low Dose is and what it is used for
2. What you need to know before you take Premique Low Dose
3. How to take Premique Low Dose
4. Possible side effects
5. How to store Premique Low Dose
6. Contents of the pack and other information

1. WHAT PREMIQUE LOW DOSE IS AND WHAT IT IS USED FOR

Premique Low Dose is a Hormone Replacement Therapy (HRT). It contains two types of female hormones, an estrogen and a progestogen (medroxyprogesterone acetate). Premique Low Dose is used to treat some of the symptoms and conditions associated with the menopause. Premique Low Dose is a period-free HRT (an HRT product where you do not have a monthly bleed).

Premique Low Dose is used for:

Relief of symptoms occurring after menopause

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

You must talk to a doctor if you do not feel better or if you feel worse.

2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE PREMIQUE LOW DOSE

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 Premique Low Dose 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 Premique Low Dose.

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

2.1 Do not take Premique Low Dose

If any of the following applies to you. If you are not sure about any of the points below, **talk to your doctor** before taking Premique Low Dose.

Do not take Premique Low Dose:

- If you are **allergic to conjugated estrogens or medroxyprogesterone acetate** 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 venous 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 are pregnant, or you are breast-feeding.

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

Warning and precautions

Talk to your doctor or pharmacist before taking Premique Low Dose. Tell your doctor 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 Premique Low Dose. 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 **2.3 - 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) (see section **2.2 – HRT and cancer** for more detail)
- high blood pressure
- heart disease (see section **2.3 – Heart Disease** for more detail)
- a liver disorder (e.g. a benign liver tumour)

- diabetes
- gallbladder disease or gallstones
- migraine or severe headaches
- fluid retention due to cardiac or kidney problems
- 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)
- low blood calcium levels (hypocalcaemia)
- a very high level of fat in your blood (triglycerides).

Stop taking Premique Low Dose 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 Premique Low Dose’ 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 rash, itching, shortness of breath, difficulty 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 **2.3 - Blood Clots in a vein (thrombosis)**.

Note: Premique Low Dose 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.

2.2 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). The **progestogen** in Premique Low Dose protects you from this extra risk.

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’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 estrogen.

Irregular bleeding

You may have irregular bleeding or drops of blood (spotting) during the first 3-6 months of taking Premique Low Dose.

However, if the irregular bleeding:

- carries on for more than the first 6 months
 - starts after you have been taking Premique Low Dose for more than 6 months
 - carries on after you have stopped taking Premique Low Dose
- **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 suggests that taking combined estrogen-progestogen and possibly also estrogen-only HRT increases the risk of breast cancer. The extra risk depends on how long you take HRT.

The additional risk becomes clear within a few years. However, it returns to normal within a few years (at most 5) after stopping treatment.

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 79 who are not taking HRT, on average, 9 to 14 in 1000 will be diagnosed with breast cancer over a 5-year period. For women aged 50 to 79 who are taking estrogen-progestogen HRT over 5 years, there will be 13 to 20 cases in 1000 users (i.e. an extra 4 to 6 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).

2.3 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 or 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 treatment with a medicine used to prevent blood clots
- if any of your close relatives has ever had a blood clot in the leg, lung or another organ
- you have systemic lupus erythematosus (SLE)
- you have cancer
- you have had a blood clot before
- you are pregnant or have recently had a baby.

For signs of a blood clot, see “Stop taking Premique Low Dose 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 are taking estrogen-progestogen HRT for over 5 years, there will be 9 to 12 cases in 1000 users (i.e. an extra 5 cases).

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.

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.

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, the figure would 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.

2.4 Other conditions

HRT will not help 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 hypertriglyceridemia (high levels of fatty substances in the blood) may experience large increases of their plasma triglycerides, which can lead to inflammation of the pancreas (pancreatitis). Symptoms of pancreatitis include sudden sharp abdominal pains, abdominal swelling, fever and feeling or being sick.

If you are taking thyroid hormone replacement therapy (e.g. thyroxine), your doctor may monitor your thyroid function more often when you start treatment.

2.5 Other medicines and Premique Low Dose

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, herbal remedies or other natural products.

Some medicines may interfere with the effect of Premique Low Dose. This might lead to irregular bleeding. This applies to the following medicines:

- Medicines for **epilepsy** (such as phenobarbital, phenytoin and carbamazepine).
- Medicines for **tuberculosis** (such as rifampicin, rifabutin).
- Medicines for **HIV infection** (such as nevirapine, efavirenz, ritonavir and nelfinavir).
- Herbal remedies containing **St. John's wort** (*Hypericum perforatum*).
- Metyrapone (most commonly used in the treatment of Cushing's syndrome).
- Aminoglutethimide (most commonly used in the treatment of breast cancer and Cushing's syndrome).

2.6 Laboratory tests

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

2.7 Pregnancy, breast-feeding and fertility

Premique Low Dose 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.

2.8 Driving and using machines

There is no evidence to suggest that Premique Low Dose will affect your ability to drive or to operate machines.

2.9 Premique Low Dose contains lactose monohydrate and sucrose

Premique Low Dose contains lactose monohydrate and sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE PREMIQUE LOW DOSE

3.1 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.

The recommended dose is one tablet every day.

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.

Take your tablet at the same time each day as this will help to remind you to take your medicine.

If you are not currently taking HRT or you are taking another period-free HRT, you may start your first pack of Premique Low Dose at any convenient time.

If you are changing from an HRT product that gives you a monthly bleed, start Premique Low Dose the day after you finish the course of the previous product, unless instructed otherwise by your doctor.

Begin your pack of Premique Low Dose by taking the first tablet marked for that day of the week. Continue to take one tablet each day following the arrows until all 28 tablets have been taken.

While you are taking Premique Low Dose you will have no tablet-free days. You should start your next pack the day after you finish the previous one.

Premique Low Dose does not cause periods. However, you may experience some irregular bleeding or light bleeding (spotting) during your first few months of taking Premique Low Dose. If the bleeding is troublesome, or continues beyond the first 3 months of treatment you should discuss this with your doctor (see section titled **Irregular bleeding** above).

Do not try to take off the coating, divide or crush the tablets as this could affect the way Premique Low Dose works.

3.2 If you take more Premique Low Dose than you should

If you take too many tablets don't worry. You may feel some nausea (sickness), breast tenderness, dizziness, abdominal pain, drowsiness, fatigue or experience a short period of vaginal bleeding, but it is unlikely that serious problems will result. If you are concerned talk to your doctor or pharmacist.

3.3 If you forget to take Premique Low Dose

If you forget to take a tablet don't worry. Take it as soon as you remember and then carry on taking the remaining tablets at the usual time.

If more than one tablet has been forgotten, do not take extra to try to make up for the forgotten tablets.

Missed tablets may cause a short period of light bleeding in women who have not had a hysterectomy.

3.4 If you need to have surgery

If you are going to have surgery make sure your doctor knows about it and/or tell the surgeon that you are taking Premique Low Dose. You may need to stop taking Premique Low Dose about 4 to 6 weeks before the operation to reduce the risk of a blood clot (see section **2.3 - Blood Clots in a vein (thrombosis)**). Ask your doctor when you can start taking Premique Low Dose again.

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

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 if HRT is started over the age of 65.

For more information about these side effects, see section 2.

Other side effects

Very common: may affect more than 1 in 10 women

- breast pain

Common: may affect up to 1 in 10 women

- breakthrough bleeding or spotting, vaginal inflammation, period pain
- breast tenderness, swollen breasts, nipple discharge
- depression
- 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, vaginal discharge
- vaginal thrush
- nausea, bloating, abdominal pain
- headache, migraine
- blood clots in the veins
- dizziness
- changes in mood including anxiety
- changes in your interest in sex (increased or decreased libido)
- visible swelling of the face or ankles
- itchininess, acne
- difficulty wearing contact lenses
- gallbladder disease (e.g. gallstones)
- hair loss

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

- vomiting
- changes in breast tissue, milky secretion from the breasts
- irritability
- allergic reactions including swelling, rash or red patches on the skin
- increase in hair growth
- an intolerance to glucose
- a worsening of asthma
- increased size of fibroids
- ovarian cancer
- worsening of epilepsy
- heart attack, stroke
- inflammation of veins just under the skin
- inflammation of the pancreas

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)
- blurred vision or loss of vision
- worsening of porphyria (a rare inherited metabolic disorder)
- growth of benign liver tumours
- increase in blood pressure.

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

The following side effects have been reported with other HRTs:

- various skin disorders:
 - painful reddish skin nodules (erythema nodosum)
 - rash with target-shaped reddening or sores (erythema multiforme)
- memory loss (dementia).

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 the Yellow Card Scheme website: www.mhra.gov.uk/yellowcard. By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE PREMIQUE LOW DOSE

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

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

Do not store above 25°C. Keep the blister in the outer carton to protect from light.

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

6.1 What Premique Low Dose contains

- The active substances are conjugated estrogens and medroxyprogesterone acetate. Each tablet contains 0.3 mg of conjugated estrogens and 1.5 mg of medroxyprogesterone acetate (MPA).
- The other ingredients are lactose monohydrate, sucrose (see section 2, Premique contains lactose monohydrate and sucrose), microcrystalline cellulose, hypromellose [(2208, K100M), (2910, E6), and (2910, E15)] , magnesium stearate, hydroxypropyl cellulose, polyethylene glycol 400, ethyl acrylate, methacrylate, titanium dioxide (E171), yellow iron oxide (E172), carnauba wax, and edible ink that contains black iron oxide (E172), propylene glycol and hypromellose.

6.2 What Premique Low Dose looks like and contents of the pack

Premique Low Dose 0.3 mg/1.5 mg Modified Release Tablets are cream coloured and are marked "PREMPRO 0.3/1.5" with black ink.

Premique Low Dose is available in packs containing 28 or 84 tablets.

Not all pack sizes may be marketed.

6.3 Marketing Authorisation Holder and Manufacturer

The Marketing Authorisation Holder is:

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
United Kingdom

The Manufacturer is:

Pfizer Ireland Pharmaceuticals
Little Connell
Newbridge

County Kildare
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