Package leaflet: Information for the patient

PREMIQUE® 0.625 mg/ 5 mg Coated 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, please 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 IS AND WHAT IT IS USED FOR

Premique is a Hormone Replacement Therapy (HRT). It contains two types of female hormones, an estrogen and a progestogen. Premique is used to treat some of the symptoms and conditions associated with the menopause.

Premique 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 alleviates these symptoms after menopause. You will only be prescribed Premique if your symptoms seriously hinder your daily life.

Prevention of osteoporosis
After the menopause some women may develop fragile bones (osteoporosis). You should discuss all available 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 Premique 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 PREMIQUE

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 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.

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

Do not take Premique

if any of the following applies to you. If you are not sure about any of the points below, t**alk to your doctor** before taking Premique.

Do not take Premique:

- If you are **allergic** (hypersensitive) to **conjugated estrogens** or **medroxyprogesterone acetate** or any of the other ingredients of Premique (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 know or suspect you are pregnant, or you are breast-feeding.

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

Warning and precautions

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. 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 an estrogen-sensitive cancer (such as having a mother, sister or grandmother who has had breast cancer) (see section 2 – HRT and cancer for more detail)
- high blood pressure
- a liver disorder, such as a benign liver tumour
- diabetes
- gall bladder 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)
- hypocalcaemia (low calcium levels)
- thyroid deficiency
- a very high level of fat in your blood (triglycerides).

Stop taking Premique 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' 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 - Blood Clots in a vein (thrombosis)

Note: Premique 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). The **progestogen** in Premique 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. However, if the irregular bleeding:

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

➢ **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 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/m^2)
- 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 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.

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 fat 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.

Other medicines and Premique

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

- 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)
- 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).

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription, herbal remedies or other natural products.

Laboratory tests

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

Pregnancy, breast-feeding and fertility

Premique is for use in postmenopausal women only. You should stop taking Premique and tell your doctor immediately if you know or suspect you are pregnant, or if you are breast-feeding.

Driving and using machines

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

Premique contains lactose monohydrate and sucrose

Premique 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

Instructions for proper use

Always take Premique exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

You may start your first pack at any convenient time. However, if you are still having periods you should start on the first day of your next period. 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.

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 will probably experience some irregular bleeding or spotting during your first few months of taking Premique. This bleeding will decrease and eventually stop completely in most women. If bleeding is troublesome or continues beyond the first 4 - 6 months of treatment, you should discuss this with your doctor.

It is best not to try to take off the coating or crush the tablets as this could affect the way Premique works. The dyes used are approved for use as food colourings. They are needed so that Premique can be identified from other tablets, and so that the different strengths of Premique can be easily recognised.

Dosage

The recommended dose is one tablet every day. You should start your new pack on the next day after you finish the old one so there will be no tablet-free days.

The tablets should be swallowed whole with some water preferably at the same time each day. This will help remind you to take your tablets.

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 such as 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 Premique for longer.

If you take more Premique than you should

If you take too many tablets by accident, do not worry, as it is unlikely that serious problems will occur. If in doubt consult your doctor or pharmacist. You may feel some nausea (sickness) or experience a short period of vaginal bleeding if you take too many tablets.

If you forget to take Premique

Do not worry if you do forget to take your tablets - just take your next tablet as soon as you remember, then carry on with your usual pill taking routine. 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**.** Always finish your current pack before starting a new one.

Missed pills may cause breakthrough bleeding.

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. You may need to stop taking Premique 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 Premique again.

If you stop taking Premique
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.

The following list of side effects have been reported in women taking HRT, each event is categorised according to how frequently an event is likely to occur:

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
- Abnormal turning out of the cervix
- Change in cervical mucus
- Vaginal Thrush
- Nausea, bloating, abdominal pain
- Headache, migraine
- Blood clots in the veins
- Dizziness
- Changes in mood including nervousness/anxiety
- Dementia (memory loss)
- Changes in your interest in sex (increased or decreased libido)
- 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)
- Hair loss

Rare: may affect up to 1 in 1,000 women
- Vomiting
- Changes in breast tissue, milky secretion from the breasts
- Allergic-like reactions
- Irritability
- Increase in hair growth
- 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
- Ovarian cancer
- Breast cancer
- Heart attack
- Blockage of arteries in the lung
- Stroke
- Worsening of epilepsy
- Increased size of fibroids
- Discoloration of the skin especially of the face or neck known as “pregnancy patches” (chloasma)

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

- Jaundice (e.g. yellowing of the skin or whites of the eyes)
- 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)
- Increase in blood pressure

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 PREMIQUE

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. Store in the original package.

If the pack has been opened or damaged return it to your pharmacist.

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 Premique contains

- The active substances are conjugated estrogens and medroxyprogesterone acetate (MPA). Each tablet contains 0.625 mg of conjugated estrogens and 5.0 mg of a progestogen, medroxyprogesterone acetate.

- The other ingredients are lactose monohydrate, sucrose (see section 2, Premique contains lactose monohydrate and sucrose), methylcellulose (E461), magnesium stearate (E572), Macrogol (E405), glyceryl mono-oleates, pharmaceutical glaze, calcium sulfate anhydrous (E516), microcrystalline cellulose, titanium dioxide (E171), povidone (E1201), carnauba wax (E903), stearic acid, calcium phosphate tribasic (E341), powdered cellulose (E460), FD&C Blue, no.2 aluminium lake HT 5625, edible ink (Opacode Black S-8-27741) †.

  †contains iron oxide black (E172), shellac (E904), purified water, ethanol, N-butyl alcohol, propylene glycol (E1520), ethyl acetate and ammonia solution.

What Premique looks like and contents of the pack

Premique coated tablets are light blue oval shaped tablets marked "0.625/5".

Premique is available in packs containing 28 coated tablets.

MARKETING AUTHORISATION HOLDER AND MANUFACTURER

The Marketing Authorisation Holder is:
Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Ireland

The Manufacturer is:
Pfizer Ireland Pharmaceuticals
Little Connell
Newbridge
County Kildare
Republic of Ireland

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