

Package leaflet: Information for the user
Climen coated tablets (2 mg; 2 mg / 1 mg)
 For use by adults only
 Estradiol valerate, cyproterone 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 any 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 Climen is and what it is used for
 2. What you need to know before you take Climen
 3. How to take Climen
 4. Possible side effects
 5. How to store Climen
 6. Contents of the pack and other information

1. WHAT CLIMEN IS AND WHAT IT IS USED FOR

Climen is a product for hormone replacement therapy (HRT). It contains two different female sex hormones, an oestrogen and a progestogen.

Climen is used for:
 Alleviation of symptoms during and after the menopause

During the menopause, the body's natural production of oestrogen declines in women. This can cause symptoms which manifest as sudden feelings of warmth over the face, neck and chest area (called hot flushes). Climen alleviates these symptoms occurring during and after the menopause, i.e. after the last menstrual period. Climen will be prescribed for you only if your symptoms interfere considerably with your everyday life.

Prevention of osteoporosis
 After the menopause, some women's bones may become brittle (osteoporosis). You should discuss all available treatment options with your doctor.
 You can use Climen to prevent osteoporosis after the menopause if you have an increased risk of osteoporosis-related bone fractures and other medicines are not suitable for you.

2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE CLIMEN

Medical history and regular check-ups
 Hormone replacement therapy is associated with risks that must be considered before the decision is taken to start or continue treatment.

Experience in the treatment of women with an early menopause (due to dysfunction of the ovaries or surgical removal of them) is limited. If you have an early menopause, the risks of hormone replacement therapy may differ from those in other women. Please ask your doctor about this.

Before you start (or resume) hormone replacement therapy, your doctor will take your personal and family medical histories. Your doctor will decide on the need for a physical examination. If necessary, this may include an examination of the breasts and/or a pelvic examination.

Once you have started hormone replacement therapy, you should visit your doctor regularly (at least once a year) for check-ups. When you attend these examinations, please discuss the benefits and risks associated with continuing treatment with Climen with your doctor.

Please attend breast screening examinations regularly, as recommended by your doctor.

Do not take Climen
 If any of the points below apply to you. If you are not sure whether this is the case, please talk to your doctor before you take Climen.

You should not take Climen

- if you are **hypersensitive** (allergic) to estradiol valerate, cyproterone acetate or any of the other ingredients of this medicine (listed in section 6)
- if you have **breast cancer** or have ever had it before or are suspected of having it
- if you have, or are suspected of having, another form of **cancer whose growth is oestrogen-dependent**, e.g. cancer of the lining of the womb (endometrium)
- if you have **unexplained vaginal bleeding**
- if you have an untreated **excess thickening of the lining of the womb** (endometrial hyperplasia)
- if a **blood clot** has developed in **one of your veins** (thrombosis) or has ever done so before, e.g. in the legs (deep vein thrombosis) or in the lungs (pulmonary embolism)
- if you have a **blood coagulation problem** (e.g. protein C, protein S or antithrombin deficiency)
- if you have ever had or currently have an illness caused by blood clots in the arteries, e.g. **heart attack, stroke or attacks of chest pain with tightness in the chest** (angina pectoris)
- if you have ever had or currently have **liver disease** and your liver function test results have not yet returned to normal
- if you have a rare inherited blood disease called **porphyria**
- if you have a **meningioma** or if a meningioma (a normally benign tumour in the tissue layer between the brain and the skull) has been detected in the past
- if you are **pregnant or breast-feeding**
- if you have ever had or currently have **liver tumours** (non-cancerous or cancerous)
- if you have a **certain fat metabolism disorder** (severe hypertriglyceridaemia)
- if you have a **particular form of progressive middle ear deafness** (otosclerosis), which worsened during a previous pregnancy

If you develop any of the above-mentioned illnesses for the first time while you are taking Climen, please stop the treatment immediately and consult your doctor promptly.

Warnings and precautions
 Talk to your doctor or pharmacist before taking Climen.

Talk to your doctor if you have ever been affected by any of the health problems listed below because they may re-emerge or become worse during treatment with Climen. In this case, you should consult your doctor more frequently for check-ups.

- non-cancerous growths in the womb (fibroids)
- growth of tissue from the womb outside the womb (endometriosis) or previous excess growth of the lining of the womb (endometrial hyperplasia)
- increased risk of developing blood clots (see "Venous blood clots (thrombosis)")
- increased risk of an oestrogen-dependent cancer (e.g. if your mother, sister or grandmother has had breast cancer)
- high blood pressure
- liver disease
- diabetes
- gallstones
- migraine or severe headaches
- an immune system disorder that interferes with a large number of organ functions in the body (systemic lupus erythematosus (SLE))
- epilepsy
- asthma
- a condition that adversely affects the eardrum and the hearing (ototoxicosis)
- fluid retention as a result of heart or kidney disease
- benign breast changes (mastopathy) and diseases
- multiple sclerosis
- Dublin-Johnson or Rotor syndrome (excretory disorders of a blood decomposition product in the bile ducts) (see below)
- a certain blood disease (sickle cell anaemia)
- jaundice, persistent itching or a rash with small blisters (Herpes gestationis) during a previous pregnancy
- chorea
- hereditary or acquired angioedema.

Close medical monitoring (including regular measurements of prolactin levels) is necessary if the patient has a non-cancerous tumour of the pituitary gland (anterior pituitary adenoma).

You must stop the treatment immediately and consult a doctor

if you experience any of the following illnesses or situations while taking hormone replacement therapy:

- illnesses mentioned in the section "Do not take Climen"
- yellowing of the skin or the whites of the eyes (jaundice), this can indicate liver disease.
- marked increase in blood pressure (symptoms can include headaches, tiredness and dizziness)
- migraine-like headache occurring for the first time
- if you become pregnant
- if you notice signs of blood clots, e.g.
 - ▷ painful swelling and redness of the legs
 - ▷ sudden chest pain
 - ▷ shortness of breath

You can find more information about this under "Venous blood clots (thrombosis)"

- increase in epileptic fits (seizures)
- sudden perceptual disorders (e.g. visual disorders, impaired hearing)
- swelling of the face, tongue and/or throat and/or difficulty swallowing or nettle rash, together with difficulties breathing, indicative of angioedema

Hormone replacement therapy and cancer
Excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the lining of the womb (endometrial cancer).

The risk of excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the lining of the womb (endometrial cancer) is increased during oestrogen-only therapy.

On average, 5 out of 1,000 women who still have a womb and who do not use hormone replacement therapy will be diagnosed with cancer of the lining of the womb between 50 and 65 years of age. Conversely, in women who still have a womb and receive hormone replacement therapy with an oestrogen product only, 10 to 60 cases of cancer of the lining of the womb per 1,000 women will be diagnosed between 50 and 65 years of age (i.e. between 5 and 55 extra cases).

To reduce this risk - it cannot, however, be completely eradicated - it is therefore important for oestrogen therapy to be combined with a progestogen in women with a womb.

As regards medications such as Climen that include progesterone for only 10 days of the cycle, there is no conclusive evidence that the risk of endometrial hyperplasia (excessive thickening of the endometrium), and endometrial carcinoma (cancer of the endometrium) could be reduced to the same extent as is the case for medications that include progesterone for 12 days of the cycle.

Unexpected bleeding
 A monthly bleed (known as a withdrawal bleed) will occur while you are taking Climen. However, if any unexpected bleeding or spotting occurs outside of your monthly bleed which

- persists beyond the first 6 months of treatment,
- starts after you have been taking Climen for more than 6 months,
- persists after you have discontinued the treatment,

please consult your doctor as soon as possible.

Breast cancer

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.

For comparison:

Women aged 50 to 54 who are not taking HRT, on average, about 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).

Examine your breasts regularly. Consult your doctor if you notice any changes in your breasts, e.g.

- puckering (dimpling) of the skin
- changes in the nipples
- lumps that you can see or feel

If you have the opportunity of taking part in a programme for early detection of breast cancer (mammography screening programme), you should take advantage of this. Tell the healthcare professional performing the mammogram that you are taking a medicine for hormone replacement treatment. Medicines taken for hormone replacement treatment can make breast tissue denser, thereby affecting the mammogram result. When breast tissue density is increased, not all changes may be detected.

Ovarian cancer

Ovarian cancer is rare - much rarer than breast cancer. The use of oestrogen-only or combined oestrogen-progestogen HRT is associated with a slightly increased risk of ovarian cancer.

The risk of developing ovarian cancer varies with age. For example, in women aged 50 to 54 who are not taking HRT, about 2 women in 2,000 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 2,000 users (i.e. about 1 extra case).

Liver tumours

Non-cancerous, and less frequently, cancerous changes to the liver have been observed in rare cases after treatment with hormonal active ingredients such as those contained in hormone replacement therapy medications. In isolated cases these changes have led to life-threatening bleeding in the abdominal cavity. You should therefore inform your doctor if you have any unusual upper abdominal symptoms that do not quickly disappear on their own.

Cardiovascular effects of hormone replacement therapy
Venous blood clots (thrombosis)

The risk of developing **blood clots in the veins** (thrombosis) is about 1.3 to 1.5 times higher in women who use hormone replacement therapy than in non-users. An increased risk exists particularly during the first few years of use.

Blood clots can have serious consequences. If a blood clot travels to the lung this can cause chest tightness, shortness of breath or collapse or even lead to death. You are more likely to develop a blood clot the older you get and if any of the following conditions apply to you. Please talk to your doctor if any of the following situations apply to you:

- if you will not be able to walk for a prolonged period of time due to major surgery, an injury or an illness (see also section 3 under "If you are scheduled to have an operation")
- if you are very overweight (BMI > 30 kg/m²)
- if you have a blood clotting problem that requires long-term medical treatment to prevent blood clots
- if a close relative of yours has ever had a blood clot in the legs, the lungs or another organ
- if you have systemic lupus erythematosus (SLE)
- if you have cancer.

For the signs of blood clots, see "You must stop the treatment immediately and consult a doctor".

For comparison:

If we take women in their 50s who do not use hormone replacement therapy, a venous blood clot will be expected in 4 to 7 in 1,000 of them, on average, over a 5-year period. There are 9 to 12 cases of thrombosis per 1,000 users (i.e. 5 additional cases) in women in their 50s who have used hormone replacement therapy with oestrogens and progestogens for 5 years.

Heart disease (heart attack)

There is no evidence that hormone replacement therapy prevents a heart attack. Women over 60 years of age who use combined hormone replacement therapy with oestrogens and progestogens have a slightly increased probability of developing heart disease compared with women who do not use hormone replacement therapy.

Stroke

The risk of stroke is about 1.5 times higher in hormone replacement therapy users than in non-users. The number of additional strokes occurring as a result of hormone replacement therapy use rises with increasing age.

For comparison:

If we look at women in their 50s who do not use hormone replacement therapy, 8 strokes per 1,000 women can be expected over a 5-year period. There are 11 cases per 1,000 users (i.e. 3 additional cases) in women in their 50s who use hormone replacement therapy.

Meningiomas

An increased risk of development of a benign brain tumour (meningioma) has been reported for higher doses of cyproterone acetates (25 mg per day and above). If a meningioma is detected in you, your doctor will discontinue all medicinal products that contain cyproterone acetate, including Climen, as a precautionary measure (see section «Do not take Climen»).

Other diseases

Hormone replacement therapy does not prevent memory disorders. There is some evidence of an increased risk of memory disorders in women who were more than 65 years of age when they started hormone replacement therapy. Ask your doctor for advice about this.

Gallbladder disease

It is known that oestrogens encourage the development of gallstones. Some women are predisposed to the development of gallbladder diseases during oestrogen therapy.

Patients with impaired kidney or heart function

Oestrogens may cause fluid retention in the body; you should therefore carefully monitor any heart or kidney function disorders you may have. You must be carefully monitored if you suffer from a severe kidney disorder, this is because the concentrations of active ingredients of Climen can be expected to increase in the blood stream.

Patients with a certain fat metabolism disorder (hypertriglyceridaemia)

If you have an increase in certain blood lipids (triglycerides), your blood lipids must be closely monitored for the duration of treatment with Climen. This is because in rare cases there have been reports of related pancreatic inflammation due to a significant increase in triglyceride in the blood during oestrogen treatment.

Uterus

Benign tumours in the muscular layer of the uterus (uterus leiomyoma / myoma) may increase in size under the influence of oestrogen. Hormone replacement therapy should be stopped if this occurs.

It is recommended that hormone replacement therapy be stopped if endometrial tissue re-appears outside the uterus (endometriosis) during treatment

Yellowish-brown skin spots (chloasma)

Yellowish-brown spots (chloasma) may occasionally appear on the skin, particularly in women who have already had them during pregnancy. Women with this predisposition should therefore avoid direct sunlight or ultraviolet light while taking Climen (e.g. sunbathing in a solarium).

Additional information for special patient groups
Children and adolescents

Climen is not indicated for use in children and adolescents.

Elderly patients

No data are available that might indicate the necessity of dose adjustment in elderly patients.

Patients with impaired liver function

Climen has not been expressly examined in patients with impaired liver function. Climen is contraindicated in women with severe liver disease (see section «Do not take Climen»).

Patients with impaired kidney function

Climen has not been expressly examined in patients with impaired kidney function.

Notes:

Climen is not a contraceptive product. If fewer than 12 months have passed since your last menstrual period or if you are under 50 years of age, additional use of birth control methods may be required. Ask your doctor for advice about this. Climen does not provide protection from AIDS.

Other medicines and Climen

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

Certain medicines can interfere with the effect of Climen. This may cause irregular bleeding. Such medicines include the following:

- medicines for **epilepsy** (e.g. barbiturates, phenytoin, primidone, carbamazepine, and possibly oxcarbazepine, topiramate and felbamate,
- medicines for **tuberculosis** (e.g. rifampicin or rifabutin),
- medicines for the treatment of **HIV infections and hepatitis C virus infections** (so-called protease inhibitors and non-nucleoside reverse transcriptase inhibitors such as nelfinavir, efavirenz, ritonavir or nelfinavir)
- herbal preparations containing **St. John's wort** (Hypericum perforatum),
- medicines for the treatment of **fungal infections** (such as griseofulvin, fluconazole, itraconazole, ketoconazole and voriconazole)
- medicines for the **treatment of bacterial infections** (e.g. clarithromycin and erythromycin)
- medicines for the **treatment of certain heart diseases or high blood pressure** (e.g. verapamil and diltiazem)
- **Ombitasvir/partaprevir/ritonavir** combination therapy with or without dasabuvir, and also **glecaprevir/pibrentasvir** therapy for hepatitis C virus (HCV) may cause elevated liver values (increase in the liver enzyme ALT) in blood tests in women using combined hormonal contraceptives containing ethinylestradiol. Climen contains estradiol instead of ethinylestradiol. It is not known whether an increase in the liver enzyme ALT can occur during use of Climen together with this combination therapy for HCV. Your doctor will be able to advise you.

► **grapefruit juice.**

This weakened effect persists for at least 4 weeks after stopping therapy with these medicines.

In rare cases, decreased estradiol levels have been observed when Climen is taken together with certain medicines to treat infectious diseases (penicillin, tetracycline). Oestrogen substances such as paracetamol may cause an increase in estradiol concentrations in the blood.

It is also possible that the need for medicines to treat diabetes (metiltus) may change.

Laboratory tests

If you require a blood test, tell your doctor or the laboratory staff that you are taking Climen because this medicine can interfere with the results of some laboratory tests.

Pregnancy and breast-feeding

Do not take Climen if you are pregnant or breast-feeding. Stop taking Climen and consult your doctor if you get pregnant during therapy. Small amounts of sex hormones can pass into breast milk.

Driving and using machines

No negative effects on driving or using machines have been observed in women using Climen.

Climen contains lactose and sucrose

Therefore, if you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking Climen.

3. HOW TO TAKE CLIMEN

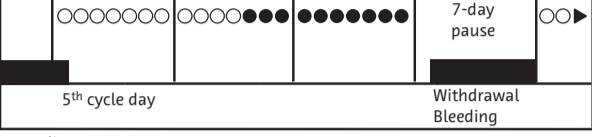
Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Your doctor will try to prescribe the lowest dose required to treat your symptoms and for the shortest time necessary. If you have the impression that the effect of Climen is too strong or too weak, talk to your doctor.

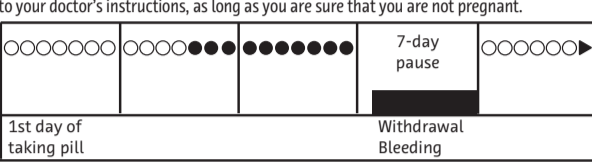
Each calendar pack of Climen contains seven self-adhesive strips marked with the days of the week to help you keep track. Select the adhesive strip which begins with the day of the week when you first take a tablet. If you are starting the tablets on, for example, a Wednesday, take the adhesive strip that begins with «WED». Stick the adhesive strip to the top edge of the Climen blister pack over the text «Apply memo-sticker here» so that the first day is over the «Start» position. The adhesive strip is as an easily understandable guide that tells you when you need to take your tablets.

Always begin with the tablet marked «Start» and continue in the direction of the arrow every day until all 21 tablets are taken. The tablets should be swallowed unchewed with liquid.

Start taking Climen on your 5th cycle day (1st day of menstruation = 1st cycle day).



○ ● Climen
 If your period appears very rarely or not at all, you can start Climen at any time according to your doctor's instructions, as long as you are sure that you are not pregnant.



○ ● Climen
 The recommended dose is:

Swallow 1 tablet whole with plenty of liquid once a day for 21 days. You will take one white tablet each day for the first 11 days, after that you will take one pink-coloured tablet each day for 10 days.

Upon completion of the 21-day treatment period, you will not take any pills during the subsequent 7-day pause, during which you will have menstruation-like withdrawal bleeding starting approximately 2 - 4 days after taking the last tablet. Unless otherwise prescribed by your doctor, after this 7-day pause you will start a new pack on the same day of the week you started your last pack.

If no bleeding occurs during the 7-day pause you must make sure that you are not pregnant before you start a new pack.

You can take Climen at any time of day, but should always take it at the same time, e.g. after breakfast.

What to do if no menstrual bleeding occurs:
 In the further course of treatment, during the pauses in pill-taking bleeding will gradually occur less often or not at all. If you think you may be pregnant you must stop taking Climen until pregnancy can be ruled out with certainty.

Please contact your doctor or pharmacist if you think the effect of Climen is too strong or too weak.

If you take more Climen than you should
 An overdose can cause nausea and vomiting and irregular bleeding. No specific treatment is necessary, but you should nevertheless consult your doctor if you are affected.

If you forget to take Climen
 If you forget to take the tablet at the usual time you should take it as soon as possible thereafter. If more than 24 hours have passed since the time you should have taken the tablet, you should not take an additional tablet to make up for the missed one.

You may experience intermenstrual bleeding if you forget to take several tablets.

If you are scheduled to have an operation
 If you are scheduled to have an operation, tell the doctor operating on you that you are taking Climen. It is possible that you will have to stop taking Climen 4 to 6 weeks before the scheduled operation in order to reduce the risk of thrombosis (see section 2 "Venous blood clots (thrombosis)"). Ask your doctor when you can continue taking Climen.

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 disorders have been reported more commonly in women who use hormone replacement therapy than in non-users:

- Breast cancer
- Excess growth or cancer of the lining of the womb (endometrial hyperplasia or cancer)
- Ovarian cancer
- Blood clots in the veins in the legs or lung (venous thromboembolism)
- Heart disease
- Stroke
- Memory disorders (dementia) if hormone replacement therapy was started over 65 years of age.

You can find more information about these side effects in section 2 under «What you need to know before you take Climen».

The following side effects, whose connection with Climen has been neither confirmed nor refuted, have been reported in hormone replacement therapy users (post-marketing data). Below is a list of possible side effects arranged in order of frequency:

- Common side effects: can occur in 1 to 10 in 100 users
- Body weight changes
- Headache
- Abdominal pain, nausea
- Skin rash (exanthema), itching
- Changes in the menstrual bleeding pattern, heavier or lighter withdrawal bleeds, intermenstrual bleeding in the form of spotting or breakthrough bleeding (this irregular bleeding usually stops with continued therapy).

Uncommon side effects: can occur in 1 to 10 in 1,000 users

- Hypersensitivity reactions
- Depressed mood
- Dizziness
- Visual disorders
- Palpitations
- Digestive disorders (dyspepsia)
- Painful reddish skin nodules (erythema nodosum), hives (urticaria)
- Breast pain, breast tenderness
- Fluid accumulation in the tissues (oedema)

Rare side effects: can occur in 1 to 10 in 10,000 users

- Anxiety, changes in libido
- Migraine
- Contact lens intolerance
- Flatulence, vomiting
- Male pattern hair growth (hirsutism), acne
- Muscle cramps
- Painful periods (dysmenorrhoea), changes in vaginal secretions, symptoms similar to premenstrual syndrome, breast enlargement
- Tiredness

In rare cases, benign liver changes have been observed after use of the hormonal ingredients contained in Climen, in addition to even rarer cases of malignant changes leading to life-threatening bleeding in the abdominal cavity. You should therefore inform your doctor if you have any unusual upper abdominal symptoms that do not quickly disappear on

