Package leaflet: information for the user

Progynova 1 mg, coated tablets
Progynova 2 mg, coated tablets
estradiol valerate

Read the entire leaflet carefully before you start using this medicine because it contains important information for you.

• Keep this leaflet. You may need to read it again.
• Do you have any questions? Please contact your doctor or pharmacist. • Do not pass this medicine on to others, as it has been prescribed for you only. It may harm others, even if their symptoms are the same as yours.
• Do you experience any side effects listed in section 4? Or do you experience a side effect not listed in this leaflet? Please contact your doctor or pharmacist.

Contents of this leaflet:

1. What is Progynova and what is it used for?

Progynova is a so-called hormone replacement therapy (HRT). It contains the female hormone estrogen. This medicine is intended for women after menopause who have not had a natural period for at least 12 months.

Progynova is used for:

Relief of symptoms after menopause
During menopause, the amount of estrogen in the female body decreases significantly. This can cause symptoms such as a warm feeling in the face, neck, and chest ('hot flashes'). Progynova relieves these symptoms after menopause. You will only be prescribed this medication if your symptoms significantly limit your daily functioning.

To prevent bone loss
After menopause, some women may develop brittle bones (osteoporosis). Your doctor will discuss the various treatments with you. If you have an increased risk of bone fractures due to bone loss and other medications are not suitable for you, you can use Progynova to prevent bone loss after menopause.

2. When should you not use this medication or be extra careful?

Medical history and regular check-ups It is important to weigh the risks of hormone replacement therapy (HRT) against the benefits before starting this medication or deciding to continue with it.

There is limited experience with treating women with premature menopause (due to ovarian problems or after surgery). If you have premature menopause, the risks of HRT use may be different. Discuss this with your doctor.

Before you start (or restart) HRT, your doctor will ask you several questions about your medical history and that of your family. Your doctor may decide to perform a physical examination and, if necessary, a breast exam and/or internal examination.

Once you have started with Progynova, you should regularly visit your doctor for check-ups (at least once a year). During these check-ups, you will discuss the pros and cons of continuing the treatment.

Have regular mammograms (X-rays) taken, according to your doctor's advice.

When should you not use this medication?
If any of the following situations apply to you, you should not use this medication. If you are unsure, consult your doctor before starting the treatment.

Do not use this medication:
• if you have or have had breast cancer, or if breast cancer is suspected
• if you have a malignant tumor that is sensitive to estrogen (e.g., a tumor of the endometrium), or if it is suspected that you have this
• if you have vaginal bleeding of unknown cause
• if you have abnormal growth of the endometrium (endometrial hyperplasia) and you are not yet being treated for it
• if you have or have ever had a blood clot in a vein (thrombosis), such as in the legs (deep vein thrombosis) or in the lungs (pulmonary embolism)
• if you have a blood clotting disorder (such as protein C, protein S, or antithrombin deficiency)
• if you have recently had a blockage in an artery or if you currently have one, such as a
• heart attack, stroke, or angina pectoris (severe chest pain due to lack of oxygen)
• if you have or have ever had liver disease and your liver function has not yet recovered
• if you have a congenital disorder in the production of red blood pigment (porphyria)
• if you are allergic to any of the ingredients in this medicine. You can find these ingredients in section 6.

If you develop any of the above conditions for the first time while using this medicine, you must stop using it immediately and contact your doctor.

When should you be extra careful with this medicine?
Contact your doctor or pharmacist before using this medicine. Before starting treatment, you should inform your doctor if you have or have had any of the following conditions, as they may recur or worsen during treatment with this medicine. If this is the case, you should visit your doctor more frequently for check-ups:
• a benign tumor in the uterus (also known as a 'fibroid')
• a condition where the uterine lining is also found outside the uterus (endometriosis)
• abnormal growth of the uterine lining (endometrial hyperplasia)
• an increased risk of blood clots (see 'Blood clot in a vein (thrombosis)')
• an increased risk of estrogen-sensitive cancer (e.g., if your mother, sister, or grandmother has had breast cancer)

• high blood pressure
• a liver disorder, such as a benign liver tumor
• diabetes
• gallstones
• migraine or severe headache
• systemic lupus erythematosus (SLE; a specific immune system disorder that can occur in many parts of the body)
• epilepsy
• asthma
• an ear disorder with hearing loss (otosclerosis) an increased fat level in your blood (triglycerides)
• fluid retention due to heart or kidney problems
• hereditary and acquired angioedema

Stop using this medicine immediately and contact your doctor
if one of the following situations occurs:
- one of the conditions under 'When should you not use this medicine?'
- yellowing of the skin or whites of the eyes (jaundice). This may be a sign of a liver disorder - swelling of the face, tongue and/or throat and/or difficulty swallowing or skin rash with pink bumps and severe itching (hives or welts), along with difficulty breathing; these symptoms indicate angioedema
- a significant increase in your blood pressure (symptoms include headache, fatigue, and dizziness) - migraine-like headache that you experience for the first time
- you become pregnant
- you notice signs of a blood clot, such as:
  - painful swelling and redness of the legs
  - sudden chest pain
  - difficulty breathing.

For more information, see 'Blood clot in a vein (thrombosis)'.

Note: Progynova is not a contraceptive. If you have had a menstrual period less than 12 months ago or are under 50 years old, you may still need to use contraceptives to prevent pregnancy. Consult your doctor for advice.

HRT and cancer
Abnormal growth of the uterine lining (endometrial hyperplasia) and cancer of the uterine lining (endometrial cancer)
Use of HRT with estrogen alone increases the risk of abnormal growth of the uterine lining (endometrial hyperplasia) and cancer of the uterine lining (endometrial cancer).

You are protected against this additional risk by taking progestogen tablets for at least 12 days of each 28-day cycle in addition to estrogen. Therefore, your doctor will prescribe progestogen separately if you still have your uterus. If your uterus has been removed, discuss with your doctor whether you can safely use this medicine without the addition of progestogen.

Of the women aged 50 to 65 who still have their uterus and do not use HRT, an average of 5 per 1000 develop endometrial cancer.

Of the women aged 50 to 65 who still have their uterus and use HRT with estrogen alone, between 10 and 60 per 1000 women develop endometrial cancer (i.e., 5 to 55 extra cases per 1000), depending on the dose and duration of treatment.

Irregular bleeding
If you use Progynova continuously sequentially (without interruption, see section 3 'How to use this medicine?'), you may experience irregular bleeding or lose small amounts of blood ('spotting') during the first 3-6 months of treatment.
However, if the irregular bleeding
• persists beyond the first 6 months
• starts after you have been using Progynova for more than 6 months
• continues after you have stopped using Progynova
• you should contact your doctor as soon as possible.

Intermenstrual bleeding
If you use Progynova cyclically (take for 3 weeks, followed by a week off, see section 3 'How to use this medicine?'), you will have a bleeding once a month (a so-called 'withdrawal bleeding'). If you experience intermenstrual bleeding or lose small amounts of blood ('spotting') in addition to your monthly bleeding, and this:
• persists beyond the first 6 months
• starts after you have been using Progynova for more than 6 months
• continues after you have stopped using Progynova, you should contact your doctor as soon as possible.

Breast cancer
Research has shown that the use of hormone replacement therapy (HRT) with an estrogen-progestogen combination or HRT with estrogen alone increases the risk of breast cancer. The extra risk depends on how long you use HRT. The extra risk occurs after 3 years of use. After stopping HRT, the extra risk will decrease again, but if you have used HRT for more than 5 years, the extra risk may persist for 10 years or longer.

Comparison
Of women aged 50 to 54 who do not use HRT, an average of 13 to 17 per 1000 will develop breast cancer over a period of 5 years.
Of women aged 50 who use HRT with estrogen alone for 5 years, there will be 16-17 cases per 1000 users (i.e., 0 to 3 extra cases).
Of women aged 50 who start HRT with an estrogen-progestogen combination over a period of 5 years, there will be 21 cases per 1000 users (i.e., 4 to 8 extra cases).
Of women aged 50 to 59 who do not use HRT, an average of 27 per 1000 will develop breast cancer over a period of 10 years.
Of women aged 50 who use HRT with estrogen alone for 10 years, there will be 34 cases per 1000 users (i.e., 7 extra cases).
Of the women aged 50 who use HRT with estrogen-progestogen combination for 10 years, there will be 48 cases per 1000 users (i.e., 21 extra cases).

➢ Regularly check your breasts. Contact your doctor if you notice any changes, such as:
• dimpling of the skin
• changes in the nipple
• lumps that you can see or feel.

You are also advised to participate in mammography screening programs (breast cancer screening) when invited. When a mammogram is taken, it is important to inform the nurse/doctor performing the mammogram that you are using HRT. HRT can increase the density of the tissue in your breasts, which can affect the outcome of the mammogram. If the density of the breast tissue is increased, it may happen that not all lumps are detected by mammography.

Ovarian cancer
Ovarian cancer is rare, much rarer than breast cancer. A slight increase in the risk of ovarian cancer has been reported with the use of estrogen therapy or a combination of estrogen/progestogen HRT. The risk of ovarian cancer depends on age. Of the women aged 50 to 54 who do not use HRT, about 2 in 2000 women are diagnosed with ovarian cancer over a period of 5 years. Among women who have used HRT for 5 years, there are about 3 cases per 2000 users (i.e., about 1 extra case).

HRT and effects on heart and circulation

Blood clot in a vein (thrombosis)
Women who use HRT have about 1.3 to 3 times higher risk of developing a blood clot in the veins than women who do not use HRT, especially during the first year of treatment.
A blood clot can be serious, and if it reaches the lungs, it can lead to chest pain, shortness of breath, fainting, and even death.

The risk of a blood clot increases as you get older and if any of the following situations apply to you. Inform your doctor in the following cases:
• you are unable to walk for a long time due to surgery, injury, or illness (see also section 3 'If you need to have surgery')
• you are severely overweight (BMI >30 kg/m2)
• you have a blood clotting disorder for which you need to use medication long-term to prevent blood clots
• one of your close relatives has ever had a blood clot in the legs, lungs, or another organ
• you have systemic lupus erythematosus (SLE)
• you have cancer.

For signs of a blood clot, see 'Stop using this medicine immediately and contact your doctor'.

Comparison
Of the women in their fifties who do not use HRT, an average of 4 to 7 out of 1000 will develop a blood clot over a period of 5 years.
Of the women in their fifties who use HRT with estrogen and progestogen for more than 5 years, there are between 9 and 12 cases per 1000 (i.e., 5 extra cases per 1000).
Among women in their fifties who have had their uterus removed and use HRT with estrogen only for more than 5 years, there are 5 to 8 cases of thrombosis per 1000 users (i.e., 1 extra case per 1000).

Heart disease (heart attack)
There is no evidence that HRT helps prevent a heart attack.

Women over 60 years old who use HRT with estrogen and progestogen have a slightly higher chance of developing heart disease than women who do not use HRT.

Women who have had their uterus removed and use HRT with estrogen only do not have a higher chance of developing heart disease.

Stroke
The risk of stroke is about 1.5 times higher in women who use HRT than in women who do not use HRT. The number of extra cases of stroke due to HRT increases with age.

Comparison
Of the women in their fifties who do not use HRT, an average of 8 out of 1000 will have a stroke over a period of 5 years. Among women in their fifties who use HRT, there are 11 cases of stroke per 1000 users over a period of 5 years (i.e., 3 extra cases per 1000).

Other conditions
• HRT does not prevent memory loss. There is evidence that there is a higher chance of memory loss in women who start using HRT after the age of 65. Ask your doctor for advice.
• Some women may experience chloasma (yellow-brown pigment spots, so-called 'pregnancy spots', especially on the face). Chloasma is particularly expected in women who have had it during pregnancy. If you have had chloasma before, you should avoid direct exposure to sunlight and ultraviolet light.

Are you using any other medicines?
Are you using any other medicines besides Progynova, or have you done so recently, or is there a possibility that you will use other medicines in the near future? Then tell your doctor or pharmacist. Your doctor will advise you. This also applies to medicines for which you do not need a prescription and herbal or natural medicines.
Some medicines reduce the effectiveness of Progynova, which may cause you to have irregular bleeding. This applies to:
• medicines for epilepsy (such as barbiturates, phenytoin, primidone, carbamazepine, and possibly oxcarbazepine, topiramate, and felbamate)
• drugs against tuberculosis (rifampicin, rifabutin)
• drugs against infections with the HIV and hepatitis C virus (so-called protease inhibitors and non-nucleoside reverse transcriptase inhibitors such as nevirapine, efavirenz, ritonavir, nelfinavir)
• herbal remedies containing St. John's wort (Hypericum perforatum)
• drugs for treating a hepatitis C virus (HCV) infection (such as the combination treatment ombitasvir/paritaprevir/ritonavir with or without dasabuvir or the treatment with glecaprevir/pibrentasvir) can cause an increase in a liver enzyme (ALT, a liver function blood test) in women using combined hormonal contraceptives with ethinylestradiol. Progynova contains estradiol instead of ethinylestradiol. It is not known whether an increase in the ALT liver enzyme can also occur when Progynova is used with this HCV combination treatment.
• drugs for the treatment of fungal infections (such as griseofulvin, fluconazole, itraconazole, ketoconazole, and voriconazole)
• drugs for the treatment of bacterial infections (such as clarithromycin, erythromycin)
• drugs for the treatment of certain heart conditions, high blood pressure (such as
• verapamil, diltiazem)
• grapefruit juice.

HRT can affect the action of some other medicines:
• a medicine against epilepsy (lamotrigine), because this can increase the risk of seizures.

Laboratory tests
If your blood is tested, you must tell the doctor or lab technician that you are using Progynova, as it can affect the results of some tests.

Pregnancy and breastfeeding
Pregnancy
Progynova is intended for use only in postmenopausal women. If you become pregnant, stop using Progynova immediately and contact your doctor.

Breastfeeding
If you are breastfeeding, you should not use Progynova.

Driving and using machines
No effects on the ability to drive and use machines have been observed in users of this medicine.

Progynova contains lactose and sucrose
If your doctor has told you that you cannot tolerate certain sugars, contact your doctor before taking this medicine.

3. How to use this medicine?
Always use this medicine exactly as your doctor or pharmacist has told you. If you are unsure about the correct use, contact your doctor or pharmacist.

The treatment can be given continuously (without interruption) or cyclically (three weeks on, followed by one week off). Continuous treatment is recommended. Your doctor will have discussed with you which of the two options is best for you.

If you have already used a cyclic or continuous sequential HRT product (both products with two different types of tablets or patches), you should start Progynova the day after the last tablet or patch of your current HRT product, unless your doctor prescribes otherwise.

If Progynova is the first HRT product you are going to use, or if you previously used a continuous combined HRT product (one type of tablet or patch for 28 days), you can decide which day is most convenient for you to start.

Take one Progynova tablet every day, without chewing, with a little water. You may take the tablets during meals or in between, as long as you take the tablets at around the same time every day.

The days of the week are printed on the strip, so you can immediately check if the daily tablet has been taken. If you start Progynova on a Wednesday, for example, take a tablet marked 'We'. Then follow the direction of the arrow on the strip until you have taken all the tablets.

Women with a uterus

Long-term use of estrogens without the addition of progestogens increases the risk of endometrial cancer in women with a uterus. To counteract this, it is necessary to use estrogens together with progestogen tablets for at least 12 days of each month.

The following treatment schedules can be applied:

Cyclic:
You take an estrogen tablet for 21 days (3 weeks), followed by a 7-day period without treatment. Your doctor will likely also give you a treatment with another hormone, a progestogen. You should take the progestogen tablets during the last 12-14 days of the 21 days you use estrogens. During the 4th week, the week in which you do not use tablets, you also do not use a medicine with progestogens. A withdrawal bleed ('menstruation') may occur during this tablet-free period.

Continuous sequential:
You take an estrogen tablet every day without interruption. Your doctor will likely also give you a treatment with another hormone, a progestogen. You should take the progestogen tablets during the last 12-14 days of the month. A withdrawal bleed ('menstruation') may occur during the period when the estrogen is combined with a progestogen.

Special patient groups
Liver insufficiency
If you have a severe liver disorder, you must not use Progynova; see also section 2 'Do not use this medicine'.

Renal insufficiency
No dosage adjustment is necessary if you have a kidney disorder.

Women without a uterus
Unless you have had a condition where the endometrial tissue is also located outside the uterus (endometriosis), if you no longer have a uterus, the estrogen treatment does not need to be combined with progestogens.

If you are using Progynova for the treatment of menopausal symptoms and you notice that Progynova is too strong or not strong enough, consult your doctor.

Duration of treatment
Your doctor will give you the lowest possible dose to treat your symptoms, for the shortest possible period. Discuss with your doctor if you think the dose is too high or too low. If you wish to stop the treatment earlier, also consult your doctor.

If you need to undergo surgery
If you need to undergo surgery, tell the doctor that you are using Progynova. You should stop using this medicine about 4 to 6 weeks before the surgery to reduce the risk of a blood clot (see section 2, 'Blood clot in a vein'). Ask your doctor when you can start using this medicine again.

Have you used too much of this medicine?
An overdose can cause nausea, vomiting, and irregular bleeding. No specific treatment is necessary, but you should ask your doctor for advice if you are concerned.

Have you forgotten to use this medicine?
If you have forgotten a tablet, you should take it as soon as possible. However, if you are more than 12 hours late, you can continue with the next tablet without taking the missed tablet. Never take a double dose of Progynova to make up for the missed dose. If you have missed multiple tablets, you may experience bleeding.

If you stop using this medicine
If you stop using Progynova, the symptoms for which Progynova was prescribed may return. Contact your doctor or pharmacist if you wish to stop using this medicine.

4. Possible side effects

Like all medicines, this medicine can have side effects, although not everyone gets them. The following conditions have been reported more frequently in women using HRT than in women not taking HRT:
• breast cancer
• abnormal growth or cancer of the endometrium (endometrial hyperplasia or cancer)
• ovarian cancer
• blood clot in a vein in the legs or lungs (venous thromboembolism)
• heart disease
• stroke
• possible memory loss when starting HRT after the age of 65.

See section 2 for more information about these side effects.

Common side effects (occur in less than 1 in 10 users):
- weight gain or weight loss
- headache
– abdominal pain, nausea
- skin rash, itching
- vaginal bleeding (sometimes spotting)

Uncommon side effects (occur in less than 1 in 100 users):
- hypersensitivity reactions
- depressed mood
- palpitations
- dizziness
- visual disturbances
- digestive disorder (dyspepsia)
- painful blue-red lumps in the skin (erythema nodosum), hives
- tender breasts, painful breasts
- fluid retention (edema)

Rare side effects (occur in less than 1 in 1,000 users):
• anxiety, decreased or increased libido (sexual desire)
• migraine
• intolerance to contact lenses
• bloating, vomiting
• excessive hair growth, acne

• muscle cramps
• dysmenorrhea (painful, sometimes also irregular menstruation), change in vaginal discharge, premenstrual-like syndrome, breast enlargement
• fatigue
The following side effects have been reported with other HRT products:
• Gallbladder disease
• Various skin conditions:
o pigmentation spots, especially on the face and neck, also known as 'pregnancy mask' (chloasma)
o painful, bluish-red nodules in the skin (erythema nodosum)
o rash with circular redness or blisters (erythema multiforme)
o vascular purpura (small pinpoint bleeding in the skin)

Reporting side effects
If you experience side effects, contact your doctor or pharmacist. This also applies to possible side effects not listed in this leaflet. You can also report side effects directly via the Netherlands Pharmacovigilance Centre Lareb, website www.lareb.nl. By reporting side effects, you can help us obtain more information about the safety of this medicine.

5 How to store this medicine?

Keep out of the sight and reach of children.

There are no special storage conditions for this medicine.

Do not use this medicine after the expiry date. It can be found on the label after Exp. It includes a month and a year. The last day of that month is the expiry date.

Do not flush medicines down the sink or toilet and do not throw them in the trash. Ask your pharmacist what to do with medicines you no longer use. They will then be destroyed responsibly and will not enter the environment.

6 Contents of the packaging and other information

What substances are in this medicine?
• The active substance in this medicine is estradiol valerate.
Each Progynova 1 mg tablet contains 1 mg estradiol valerate.
Each Progynova 2 mg tablet contains 2 mg estradiol valerate.
• The other substances in this medicine are:
lactose monohydrate, maize starch, povidone 25,000, talc (E553b), magnesium stearate (E470b), sucrose, povidone 700,000, macrogol 6000, calcium carbonate, montan glycol wax (Cera E). In Progynova 1 mg: additionally: glycerol 85%, titanium dioxide (E171), and iron oxide yellow (E172).

What does Progynova look like and what is in a package?
Progynova tablets are coated tablets; the core of the tablet is coated with a sugar layer.
• The Progynova 1 mg tablets are beige,
• The Progynova 2 mg tablets are white.
Progynova 1 mg and Progynova 2 mg are available in packages with 3 PVC AL blister packs of 28 tablets. Progynova 1 mg contains in a strip 28 beige tablets each with 1 mg estradiol valerate. Progynova 2 mg contains in a strip 28 white tablets each with 2 mg estradiol valerate.

Marketing authorization holder and manufacturer

Registration holder/repacker
BModesto B.V.
Minervaweg 2
8239 DL Lelystad

Manufacturers
Progynova 1 mg:
Bayer AG
Müllerstraße 178
13353 Berlin
Germany

Progynova 1 mg and 2 mg:
Bayer Weimar GmbH und Co. KG
Döbereinerstraße 20
99427 Weimar
Germany

Registered under:
RVG 132305/05861 - Progynova 1 mg, coated tablets. Country of origin: Belgium.
RVG 132304/05311 - Progynova 2 mg, coated tablets. Country of origin: Belgium.

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