Package leaflet: information for the user
Primolut N, tablets 5 mg

norethisterone

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? Contact your doctor or pharmacist.
- Do not pass this medicine on to others, as it has been prescribed only for you. It may harm them, 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? Then contact your doctor or pharmacist.

Contents of this leaflet

1. What is Primolut N and what is it used for?

Primolut N belongs to the synthetic progestogens. These are hormones that have an effect similar to the progesterone produced by the female body itself. They have the ability to shed the uterine lining built up under the influence of estrogens.

Primolut N is used for:
- Dysfunctional uterine bleeding
  These are irregular bleedings, which mainly occur in young girls and women in the transitional years.
- Amenorrhea (absence of menstruation)
  If a woman has never had a menstruation, this is called primary amenorrhea. If there were menstruations in the past, but later they stopped for a longer period consecutively, it is a case of prolonged secondary amenorrhea.
- Endometriosis
  This is a condition where the tissue (called endometrium) that normally only lines the inside of the uterus is also found in other, unusual places (for example, the ovaries). By using Primolut N, the mucous membrane at the unwanted places shrinks.
- The shifting of menstruation.

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

When should you not use this medicine?

You should not use this medicine:

- if you are pregnant or suspect you might be pregnant
- if you are breastfeeding

- if you have or have had a severe liver disease. Discuss the use of Primolut N in this case with your doctor. Primolut N should only be used once your liver function values have returned to normal.
- if you have or have had a tumor (benign or malignant) in the liver
- if you have (or have ever had) a blood clot in a blood vessel of a leg (thrombosis), a lung (pulmonary embolism), or another organ
- if you have (or have ever had) a heart attack or stroke
- if you have a condition that may be a precursor to a heart attack (for example, angina pectoris, which causes severe chest pain) or a stroke (for example, a transient ischemic attack without residual symptoms), or have ever had
- if you have a severe risk factor or multiple risk factors for the formation of blood clots
- if you have a bleeding disorder (for example, protein C deficiency)
- if you have or have had a certain type of migraine (with so-called focal neurological symptoms such as symptoms related to vision, speech impairment, or weakness or numbness in a part of the body)
- if you have diabetes and have damaged blood vessels
- if you have breast cancer or cancer of the reproductive organs (or have ever had it), or if it is suspected that you have it
- if you have vaginal bleeding of unknown cause
- if you are allergic to any of the ingredients in this medicine. You can find these ingredients in section 6.

Do not use Primolut N if you have hepatitis C and are taking medicines containing ombitasvir/paritaprevir/ritonavir and dasabuvir (see also section 2 'Are you taking any other medicines?').

When should you be extra careful with this medicine?

The sex hormone (progesterone) contained in this product is partially converted to estrogen. Therefore, the general warnings associated with the use of combined oral contraceptives (combination pills) should also be considered with Primolut N.
In some cases, you need to be extra careful when using Primolut N. It may be necessary for you to be regularly monitored by your doctor. Contact your doctor before you start using Primolut N if any of the following situations apply to you or if any of the conditions below occur or worsen during the use of Primolut N:

- if you smoke
- if you have diabetes (metabolic disease with elevated blood sugar levels)
- if you are severely overweight
- if you have high levels of fat in your blood (hypertriglyceridemia) or this condition runs in your family. Hypertriglyceridemia is associated with an increased risk of developing pancreatitis (inflammation of the pancreas).
- if you have high blood pressure
- if you have a heart valve disorder or a certain heart rhythm disorder

- if you have had thrombosis or embolism
- if any of your close relatives have had thrombosis (venous thromboembolism in a brother, sister, or parent at a relatively young age), a heart attack, or stroke at a young age
- if you have inflammation of the blood vessels (superficial thrombophlebitis)
- if you have varicose veins
- if someone in your immediate family has had breast cancer
- if you or someone in your immediate family has had high levels of cholesterol or triglycerides (fatty substances) in the blood
- if you have liver disease or gallbladder disease
- if you have Crohn's disease or ulcerative colitis (chronic inflammation of the intestines)
- if you have systemic lupus erythematosus (SLE, an immune system disease)
- if you have hemolytic uremic syndrome (HUS, a blood clotting disorder that causes kidney failure)
- if you have sickle cell disease (a hereditary disorder of the red blood cells)
- if you have a condition that first occurred or worsened during pregnancy or previous use of sex hormones (e.g., hearing loss, a metabolic disorder called porphyria, a skin disease called herpes gestationis, or a neurological disease called Sydenham's chorea)
- if you have hereditary angioedema. Contact your doctor immediately if you have symptoms of angioedema such as a swollen face, tongue and/or throat, and/or difficulty swallowing, or a rash accompanied by difficulty breathing. Medicines containing estrogen can cause or worsen symptoms of angioedema.
- if you suffer from heart failure (insufficient pumping action of the heart), liver or kidney dysfunction, epilepsy, or migraine. Discuss this with your doctor, due to the risk of sodium (salt) and water retention.
- if you are sensitive to male sex hormones (androgens). Animal studies have shown that norethisterone, the active ingredient of Primolut N, can also cause male characteristics to a small extent. It is therefore not entirely excluded that, in women who are sensitive to this, mild symptoms of masculinization may occur.
- if approximately 3 days after stopping the tablets no bleeding has occurred. You should then inform your doctor. If it is necessary to continue the treatment, pregnancy must first be ruled out before resuming the treatment (see "How to use this medicine?").
- if you have had a mental depression in the past. Your doctor will monitor you carefully. If the depression returns severely, treatment with Primolut N should be stopped.

Some women may experience chloasma (yellow-brown pigment spots, so-called 'pregnancy spots', especially on the face) while using Primolut N. 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 while using Primolut N.

Your doctor will discuss the pros and cons of Primolut N with you.

Before you start or resume treatment, your doctor may examine you. If the treatment is continued for a longer period, regular examination is recommended. The frequency and nature of this examination will be tailored to your personal situation.
Primolut N and blood clots in veins and arteries (thrombosis)

Thrombosis is the formation of a blood clot that can block a blood vessel.

Epidemiological studies have shown that the use of contraceptive pills containing estrogen and progestogen in women increases the risk of developing a blood clot in a vein (venous thrombosis) compared to women who do not use contraceptive pills.

Thrombosis sometimes occurs in the deep veins of the legs (deep vein thrombosis). Venous thromboembolism (VTE) can develop, whether or not in connection with the use of the contraceptive pill. It can also occur if you are pregnant. If a blood clot breaks loose from the vein where it formed, it can reach the arteries of the lungs and block them, causing a pulmonary embolism. Blood clots can also very rarely occur in the blood vessels of the heart (and cause a heart attack cause). Blood clots or a ruptured blood vessel in the brain can cause a stroke.

Research has shown that in women using a low-dose 'combination pill' (contraceptive pill with less than 50 micrograms of the estrogenic hormone ethinylestradiol), there are up to 40 cases of venous thrombosis per 100,000 woman-years (1 woman-year of pill use is 1 woman using a combination pill for 1 year). In women who do not use a combination pill, this is 5-10 cases per 100,000 woman-years. During pregnancy, the number of cases is estimated at 60 cases per 100,000 pregnancies.

During the use of combination pills, venous thromboembolism, which manifests as deep vein thrombosis and/or pulmonary embolism, can occur.

In extremely rare cases, blood clots can occur in other parts of the body, including the liver, intestines, kidneys, brain, or eyes.

The risk of thromboembolism is also increased shortly after the birth of the child.

Blood clots can rarely occur in the blood vessels of the heart (causing a heart attack) or the brain (causing a stroke).

The risk of venous thrombosis with the use of a combination pill increases:

- as you get older
- if you are overweight
- if one of your close family members has had a blood clot in a leg (thrombosis), lung (pulmonary embolism), or other organ at a young age
- if you have to stay in bed for a long time or are not allowed to walk (for example, with a leg in a cast or splint), if you have to undergo major surgery, any surgery on the legs, or if you have had a serious accident. In these cases, it is better to stop using Primolut N (if surgery is planned, you should stop at least four weeks in advance) and not start again until two weeks after you are fully mobile again.

Very occasionally, thrombosis can cause serious permanent disabilities or even be fatal.

The use of combination pills has been associated with an increased risk of a blood clot in an artery (arterial thrombosis), for example in the blood vessels of the heart (heart attack) or the brain (stroke).

The risk of arterial thrombosis with the use of a combination pill increases:

- if you smoke. You are strongly advised to stop smoking if you use a combination pill, especially if you are over 35 years old.
- if you have or have had a high level of cholesterol or triglycerides (fatty substances) in the blood.
- if you are overweight
- if you or one of your close family members has had a heart attack or stroke at a young age
- if you have high blood pressure. If you develop high blood pressure while using Primolut N, you may be advised to stop using it
- if you have migraines
- if you have heart problems (a heart valve condition, arrhythmia).

Primolut N and cancer

In women who use a combination pill, breast cancer is diagnosed slightly more often, but it is not clear whether this is caused by the use of the pill. For example, it may also be that more breast cancer is detected in women who use a combination pill because they are examined more often by their doctor. The risk of breast cancer gradually decreases after stopping a combination pill. It is important to regularly check your breasts. If you feel a lump, you should contact your doctor.

In rare cases, benign liver tumors have been found in users of hormonal substances such as those in Primolut N, and in even rarer cases, malignant liver tumors. These tumors can lead to internal bleeding.

The most important risk factor for cervical cancer is a long-term infection with the so-called human papillomavirus (HPV). Some studies suggest that the use of the contraceptive pill by the user in the long term increases the risk of developing cervical cancer. However, this may not be due to the contraceptive pill but may be related to sexual behavior and other factors. It is not yet clear how significant the influence of this is on getting cervical cancer.

The aforementioned tumors can be life-threatening and have a fatal outcome.

If you suddenly experience severe abdominal pain, you should contact your doctor immediately.

Stop taking this medicine immediately if:

- you experience severe headaches or (for the first time) migraine-like headaches
- you experience visual disturbances, such as flickering before the eyes
- you experience sudden hearing disturbances
- you experience unusual pain in or swelling of limbs, stabbing pain when breathing, coughing without a clear cause, pain or tightness in the chest. These are symptoms that may indicate thrombosis (formation of a blood clot in a blood vessel) or a pulmonary embolism (blood clot in a blood vessel of the lung)
- you know you need to have surgery (6 weeks in advance) or if you have to stay in bed for a long time (e.g., after an accident)
- you develop hepatitis accompanied by jaundice (yellowing of the skin or eyes)

- you experience itching all over the body
- your blood pressure rises significantly
- you become pregnant
- you suffer from severe pain in the upper abdomen.
  In rare cases, after administration of hormones such as norethisterone, benign and in very rare cases malignant changes of the liver have been observed that have led to life-threatening bleeding in the abdominal cavity. It is important that you consult your doctor if you experience unusual symptoms in the upper abdomen that do not quickly resolve on their own.

Consult your doctor if any of the above warnings apply to you, or have applied in the past.

Are you using any other medicines?

Are you taking any other medicines in addition to Primolut N 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. This also applies to medicines that you can obtain without a prescription.

During the use of Primolut N, the need for blood sugar-lowering agents (oral anti-diabetics or insulin) may change in diabetic patients.

Some medicines
- can affect the blood levels of Primolut N
- can cause this medicine to work less effectively
- can cause unexpected bleeding.

These include:
- medicines for the treatment of:
  - epilepsy (for example, primidone, phenytoin, barbiturates, carbamazepine, oxcarbazepine, topiramate, or felbamate)
  - tuberculosis (for example, rifampicin)
  - infections with the HIV and hepatitis C virus (so-called protease inhibitors and non-nucleoside reverse transcriptase inhibitors such as ritonavir, nevirapine, efavirenz).
  - fungal infections (griseofulvin, azole antifungals, such as itraconazole, voriconazole, fluconazole)
  - bacterial infections (macrolide antibiotics, such as clarithromycin, erythromycin)
  - certain heart diseases, high blood pressure (calcium channel blockers, such as verapamil, diltiazem)
  - arthritis, osteoarthritis (etoricoxib)
  - high blood pressure in the pulmonary blood vessels (bosentan).
- the herbal remedy St. John's wort (is mainly used for the treatment of depressive moods)
- grapefruit juice.

Primolut N can affect the action of other medicines, for example:
- medicines containing cyclosporine
- the anti-epileptic drug lamotrigine (this can lead to an increased number of seizures)

- theophylline (used in the treatment of respiratory problems)
- tizanidine (used in the treatment of muscle pain and/or muscle cramps).

Do not use Primolut N if you have hepatitis C and are using medicines containing ombitasvir/paritaprevir/ritonavir and dasabuvir, as this may cause an increase in the ALAT liver enzyme (a liver function blood test). Approximately two weeks after the end of this treatment, you can start using Primolut N again. See section 2 'When should you not use this medicine?'.

If you are having a blood test, you must tell your doctor or the laboratory staff that you are using Primolut N as this may affect the results of some tests.

Pregnancy and breastfeeding

Are you pregnant, do you think you might be pregnant, do you want to become pregnant, or are you breastfeeding? Then contact your doctor or pharmacist before using this medicine.

If you are pregnant, you should not use Primolut N. If you become pregnant while using it, you must stop taking Primolut N immediately and inform your doctor.
If you are breastfeeding, you should not use Primolut N.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

There are no reasons to assume that Primolut N affects this.

Primolut N contains lactose

If you are hypersensitive to certain sugars, you should contact your doctor before using Primolut N.

3. How to use this medicine?

Always take this medicine exactly as your doctor has told you. If you are unsure about the correct use, contact your doctor or pharmacist.
Take the tablets with sufficient liquid (for example, a glass of water). To prevent nausea, it is recommended to take the tablets after a meal.

NOTE
You must ensure that no pregnancy can occur during the entire treatment with Primolut N. It is therefore necessary to use a non-hormonal contraceptive. Consider, for example, a condom. If no withdrawal bleeding occurs during the treatment at regular intervals of about 28 days, pregnancy should be considered. As long as there is no certainty about this, the treatment must be stopped.

The dosage depends on the condition for which you are prescribed Primolut N. You can find the correct dosage below under the relevant heading.

Dysfunctional (irregular) bleeding

Take 3 tablets per day for 10 days. The bleeding generally stops within 1 to 3 days. However, in some cases only after 5 days. For a good result of the treatment, it is necessary to continue taking Primolut N regularly even after the bleeding stops (a total of 30 tablets for the 10-day treatment). Approximately 2 to 4 days after ending the treatment, a bleeding occurs that is comparable in strength and duration to a menstruation. Such bleeding is also called a withdrawal bleeding.

Although your doctor has prescribed Primolut N to stop the irregular bleeding, it is possible that you still experience irregular blood loss during the first treatment cycles. The following situations are possible:

- Light bleeding during treatment
  Occasionally, after the bleeding has initially stopped, light blood loss may occur again. However, you should not stop taking the tablets. Light bleeding usually stops on its own. In case of heavy or repeated blood loss during intake, you should consult your doctor.

- Failure to stop the bleeding; heavy breakthrough bleeding
  If you take your tablets regularly, but the bleeding does not stop, it is important to inform the treating doctor immediately as other

- measures are necessary in most cases. This also applies if you experience strong bleeding again (breakthrough bleeding) during tablet intake after the bleeding initially stopped.

- Prevention of recurrence of dysfunctional bleeding
  To prevent recurrence of dysfunctional bleeding, you should take 1 to 2 tablets of Primolut N daily from the 16th to the 25th day of the cycle during the next 3 cycles (the first day of the cycle is the first day of the last withdrawal bleeding). A few days after you stop taking Primolut N, you will experience a withdrawal bleeding again.

Amenorrhea (absence of menstruation)
To promote the growth of the uterine lining, your doctor has also prescribed an estrogen. Start with the estrogen as prescribed by your doctor and then take 1 to 2 tablets of Primolut N per day from the 16th to the 25th treatment day. However, if your estrogen production is sufficient, you can try to omit the estrogen and take 2 tablets of Primolut N per day from the 16th to the 25th cycle day.
A few days after you stop taking Primolut N, a withdrawal bleeding occurs (approximately on the 28th treatment day).

Endometriosis
Start the treatment between the 1st and the 5th cycle day (the 1st cycle day is the 1st day of your menstruation). Take 1 tablet of Primolut N twice a day. If light bleeding (spotting) occurs during the treatment, your doctor will double the dose (2x2 tablets). After the spotting disappears, the dose can be returned to the previous level. The treatment duration should be at least 4 to 6 months. A few days after you stop taking Primolut N, you will experience a withdrawal bleed.

Postponement of menstruation
The monthly bleeding can be advanced or delayed if there are valid reasons.

- Advancing the bleeding
  To advance a bleeding, your doctor will preferably prescribe a medication that contains both a progestogen and an estrogen. Because such a medication generally prevents ovulation, pregnancy is virtually excluded.

- Delaying the bleeding
  Since Primolut N must be taken at such a time in the cycle to delay menstruation that pregnancy cannot be definitively excluded, you can only use this method if you are sure you are not pregnant.

  Take 1 tablet of Primolut N 2 to 3 times a day starting about 3 days before the expected menstruation. Do not use Primolut N for more than 10-14 days. Two to three days after you stop taking Primolut N, you will experience a withdrawal bleed.

If you notice that Primolut N is too strong or too weak, you should ask your doctor or pharmacist for advice.

Have you taken too much of this medicine?
If you have taken too much Primolut N, contact your doctor or pharmacist immediately.

There are no known direct harmful effects of an overdose of Primolut N. However, it can lead to nausea, vomiting, and irregular bleeding. No special treatment is necessary.

Have you forgotten to take this medicine?
Take the missed dose as soon as possible if it is not yet time for the next dose. Do not take a double dose to make up for a forgotten dose.
If you do not take a tablet for several consecutive days, you will experience irregular bleeding.

If you stop taking this medicine
If you stop taking Primolut N, it is possible that the symptoms will return.

Do you have any other questions about the use of this medicine? Then contact your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everyone gets them.

Below is a list of side effects that may occur.

Very common side effects (occur in more than 1 in 10 users):
- Bleeding from the uterus/vagina and breakthrough bleeding*
- Too little menstruation (hypomenorrhea)

Common side effects (occur in less than 1 in 10 users):
- Headache
- Nausea
- Vomiting
- Absence of menstruation (amenorrhea)*
- Fluid retention in the body (edema)

Uncommon side effects (occur in less than 1 in 100 users)
- Migraine

Rare side effects (occur in less than 1 in 1,000 users)
- Hypersensitivity reactions
- Change in liver function values
- Jaundice (yellowing of the skin or whites of the eyes)
- Skin rash with severe itching and bumps (hives, urticaria)

Very rare side effects (occur in less than 1 in 10,000 users)
- Visual disturbances, such as flickering before the eyes
- Shortness of breath (dyspnea)

* With continuous use

Additionally, a change in libido (increased or decreased sexual desire) may occur.
With prolonged administration and high dosages, acne, depressive moods, water and salt retention, weight gain, and excessive hair growth (hirsutism) may occur.

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.
Store in the original packaging to protect against moisture. Store below 25°C.

Do not use this medicine after the expiry date. You can find it on the packaging 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 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 norethisterone. Each tablet contains 5 mg of norethisterone.
- The other substances in this medicine are: lactose monohydrate, maize starch, and magnesium stearate.

What does Primolut N look like and what is in a package?
The tablets have a cross score and are therefore divisible. Primolut N is available in packages of 30 tablets.

Marketing authorization holder and manufacturer

Registration holder
Bayer B.V.
Siriusdreef 36
2132 WT Hoofddorp

For information:
Bayer B.V., P.O. Box 88, 2130 AB Hoofddorp

Manufacturer
Bayer AG Germany and Bayer Weimar GmbH und Co. KG 13342 Berlin, Weimar, Germany

Primolut N is registered in the drug register under RVG 02179

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