Package leaflet: Information for the user
Primolut® N 5 mg tablets
Norethisterone

Read all of this leaflet carefully before you start taking Primolut N tablets 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 Primolut N IS AND WHAT IT IS USED FOR

Primolut N is a so called progestin preparation, i.e. a synthetic hormone preparation that has similar properties to progesterone, which is a natural female hormone.

Primolut N is used to treat various kinds of bleeding disorders and absence of menstruation (amenorrhea) caused by various reasons, to alleviate symptoms of premenstrual syndrome, to treat mastopathy, to postpone menstruation, and to treat endometriosis.

Primolut N contains norethisterone which can sometimes be used in the treatment of illnesses other than the ones mentioned in this leaflet. Ask your doctor, pharmacist or other healthcare professional for advice, if necessary, and always follow their instructions.

2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE PRIMOLUT N

Do not use Primolut N :
- if you are allergic to norethisterone or to any of the other ingredients of this medicine (listed in section 6)
- if you are pregnant or think you may be pregnant
- if you are breast-feeding
- if you have or have had a heart attack or stroke) caused by a blood clot or a ruptured vein in the brain)
- if you have or have had a condition that may be a preliminary symptom of a heart attack (e.g. angina pectoris, which causes severe chest pain and may radiate in the left arm) or stroke (e.g. transient ischemic attack, which leaves no permanent effects)
- if you have several risk factors for a blood clot
- if you have or have had a certain type of migraine (which is associated with so called focal neurological symptoms such as visual disturbances, speech difficulties or weakness or numbness in some part of the body)
- if you have diabetes with blood vessel damage
- if you have or have had a severe liver disease and the doctor has told you that your liver function is not yet back to normal; symptoms of liver disease include jaundice and/or itching all over the body

- if you have or have had a benign or malignant liver tumor
- if you have or have had a malignant tumor that may grow under the influence of sex hormones, such as breast cancer or cancer of the genital organs.

Do not use Primolut N if you have hepatitis C and are taking the medicinal products containing the combination of ombitasvir / paritaprevir/ritonavir and dasabuvir (see also section Other medicines and Primolut N).
If any of these diseases or conditions appears for the first time while you are using Primolut N tablets, stop taking them and contact your doctor.

Warnings and precautions
Talk to your doctor or pharmacist before using Primolut N.
The sex hormone (progestin) contained in this product is transformed partly into estrogen. Therefore, any general warnings related to the use of combined contraceptives must also be taken into account in addition to the warnings related to Primolut N tablets.

Under certain circumstances during the use of Primolut N special caution is necessary. Regular check-ups may be required. Contact your doctor before you start taking Primolut N if any of the conditions listed below apply to you or if any of them appears or worsens when you take this medicine:
- if you smoke
- if you have diabetes (a metabolic disease with elevated blood sugar levels)
- if you are very overweight
- if you have high blood pressure
- if you have valvular heart disease or a certain type of arrhythmia (atrial fibrillation)
- if you have had a blood clot
- if any of your immediate family has had a blood clot (venous thromboembolism in a sibling or parent at a relatively young age), heart attack or stroke at a young age
- if you have a superficial inflammation of your veins
- if you have varicose veins
- if you or any of your immediate family has had a breast cancer
- if you have or have had liver spots (golden brown skin pigmentation especially on the face); avoid overexposure to sunlight and ultraviolet radiation
- if you have had depression
- if you have migraine
- if you have epilepsy (see section “Other medicines and Primolut N”)
- if you have elevated levels of fat in the blood (hypertriglyceridemia) or a positive family history for this condition. Hypertriglyceridemia has been associated with an increased risk of developing an inflammation of the pancreas (pancreatitis).
- if you have a liver or gallbladder disease
- if you have Crohn's disease or ulcerative colitis (a chronic inflammation of the colon)
- if you have SLE (systemic lupus erythematosus, a condition of the immune system)
- if you have HUS (hemolytic uremic syndrome, a disorder of blood coagulation causing kidney failure)
- if you have sickle cell anemia
- if you have a condition that has appeared for the first time or worsened during pregnancy or previous use of sex hormones, e.g .impairment of hearing, porphyria (a metabolic disease), herpes gestationis (a skin disease) or Sydenham's chorea (a neurological disease)
- if you have hereditary angioedema. Contact your doctor immediately if you experience symptoms of angioedema such as swollen face, tongue or pharynx and/or difficulty swallowing or hives together with difficulty in breathing. Products containing estrogen may cause or aggravate these symptoms of angioedema.
- **Contact your doctor if any of the above conditions appears for the first time, recurs or worsens while you are using Primolut N.**

Primolut N and thrombosis

Thrombosis is a blood clot inside a vein and it may block the vein.

Research results indicate that the use of oral contraceptives containing estrogen and progestin increases the risk of developing a blood clot compared with women who are not using any oral contraceptives .

A blood clot may appear in the deep veins of the leg (deep venous thrombosis). A venous thrombosis may develop even if you are not using oral contraceptives. It can also develop during pregnancy. If a blood clot starts moving from the vein where it was formed, it may travel into the veins in the lungs, block them and cause a blood clot in the lung (pulmonary embolism). Blood clots may in rare cases also appear in the veins of the heart and cause a heart attack. A blood clot or a ruptured vein in the brain can cause a stroke.

The total risk of venous thromboembolism in users of combined estrogen products (low estrogen dose, less than 50 micrograms ethinyl estradiol) is 2-3 -fold compared with the risk in non-users who are not pregnant. The increased risk is smaller than that associated with pregnancy or childbirth.

Venous thromboembolism manifesting as a deep venous thrombosis and/or pulmonary embolism can occur during the use of any combined contraceptive.

In extremely rare cases blood clots may appear in other organs as well such as the liver, intestines, kidneys, brain, or eyes.

The risk of a blood clot is also increased immediately after childbirth.

WHEN TO CONTACT YOUR DOCTOR?

Regular check-ups

- When you are using Primolut N, your doctor will tell you when to come for regular check-ups.

Contact your doctor as soon as possible if

- you notice any changes in your health, especially if the changes are related to issues mentioned in this package leaflet (see also sections “Do not use Primolut N” and ”Warnings and precautions”; do not forget the factors related to your immediate family)
- you feel a lump in your breast
- you intend to use other medications (see also section “Other medicines and Primolut N”)
- you are immobilized for a longer period of time or have surgery scheduled (contact your doctor at least six weeks in advance)
- you have unusual, heavy vaginal bleeding.

Stop taking Primolut N and contact your doctor immediately if you notice any signs of thrombosis, such as:

- coughing without a clear reason
- a feeling of pain and pressure in the chest; the pain may radiate to your left arm
- breathlessness
- more and more frequent occurrence of exceptionally severe and prolonged headache or first-time occurrence of a migraine attack
- partial or complete loss of vision, or double vision
- slurring or speech disability
- sudden changes in your hearing, sense of smell, or taste
- dizziness or fainting
- weakness or numbness in some part of the body
- severe pain or swelling in either of your legs.

Stop using Primolut N and contact your doctor immediately also if

- you have jaundice (yellowish skin and whites of your eyes; these can be signs of a liver inflammation)

- you have generalized severe itching
- you have high blood pressure
- you are pregnant.

The situations and symptoms mentioned above are described and explained in more detail elsewhere in this leaflet.
The risk of venous or arterial blood clot (e.g. deep venous thrombosis, pulmonary embolism, heart attack) or stroke increases:

- with age
- if you are overweight
- if you or any of your immediate family have or have had a blood clot (in the leg, lung or elsewhere in the body), heart attack or stroke at a young age; or if you or any of your relatives have or is suspected of having a hereditary condition that causes blood clots, you are at an increased risk of developing a blood clot. In such a case, talk to a specialist before you start using combined oral contraceptives. Certain blood related factors that may indicate a predisposition for venous or arterial thrombosis include APC (activated protein C) resistance, hyperhomocysteinemia, antithrombin III deficiency, protein C and S deficiency, antiphospholipid antibodies (cardiolipin antibody, lupus anticoagulant).
- if you need to be immobilized for a long time (e.g. you have a leg plaster or splint), you are scheduled for a major surgery or any surgery to legs, or you have had a serious accident. In these situations it is advisable to discontinue the use of oral contraceptives (at least four weeks in advance) and not resume until two weeks after complete remobilization .
- if you smoke (the risk increases with heavy smoking and age, especially in women over 35 years of age). Stop smoking if you are using oral contraceptives, especially if you are older than 35 years of age.
- if you or any of your immediate family have or have had high blood cholesterol or triglyceride levels (fatty substances in blood).
- if you have high blood pressure. If you develop high blood pressure while using oral contraceptives, you may be told to stop using them.
- if you have migraine
- if you have valvular heart disease or a certain type of arrhythmia (atrial fibrillation).
- In very rare cases blood clots may cause serious permanent disability or may even be fatal.
- **If you notice any signs of thrombosis, stop using Primolut N and contact your doctor immediately**) **.**See also section “When to contact your doctor?”)

<u>Primolut N and cancer</u>
Breast cancer has been diagnosed slightly more often in women using combined oral contraceptives but its relationship with the use of combined oral contraceptives is not known. Women who are using combined oral contraceptives have more regular check-ups, and it is possible that tumors are therefore found more frequently. The prevalence of diagnosed breast tumors decreases after the discontinuation of combined oral contraceptive use. It is important that you examine your breasts regularly and contact your doctor in case you notice a lump.

In rare cases benign liver tumors, and even more rarely malignant liver tumors, have been reported in users of preparations that contain the same hormone as Primolut N. These tumors may lead to internal bleeding.

The most important risk factor for cervical cancer is a prolonged human papilloma virus (HPV) infection.

An increased risk of cervical cancer in long-term users of combined oral contraceptives has been reported in some studies, but there continues to be controversy about the extent to which this finding is influenced by sexual behavior or other risk factors related to the papilloma virus .

The tumors mentioned above can be life-threatening or fatal.

- **Contact your doctor immediately if you have severe pain in your abdomen.**

Other medicines and Primolut N
Some medicines :
- can have an influence on the blood levels of Primolut N
- can make Primolut N less effective
- can cause unexpected bleeding.

These include:
- medicines used for the treatment of the following diseases:
  - epilepsy (e.g. primidone, phenytoin, barbiturates, carbamazepine, oxcarbazepine, topiramate, felbamate)
  - tuberculosis (e.g. rifampicin)
  - HIV and Hepatitis C virus infections (so-called protease inhibitors and non-nucleoside reverse transcriptase inhibitors, e.g. ritonavir, nevirapine, efavirenz)
  - fungal infections (griseofulvin, azole antifungals, e.g. itraconazole, voriconazole, fluconazole)
  - bacterial infections (macrolide antibiotics, e.g. clarithromycin, erythromycin)
  - certain heart diseases, high blood pressure (calcium channel blockers, e.g. verapamil and diltiazem)
  - arthritis, arthrosis (etoricoxib)
  - high blood pressure in the blood vessels in the lung (bosentan)
- herbal remedies containing St. John's wort (oririginally used for the treatment of depressive moods)
- grapefruit juice.

Primolut N may influence the effect of some medicines. These include, for example:
- medicines containing cyclosporine
- the anti-epileptic lamotrigine (concomitant use can lead to an increased frequency of epileptic seizures)
- theophylline (used to treat breathing problems)
- tizanidine (used to treat muscle pain and/or muscle cramps).

Do not use Primolut N if you have Hepatitis C and are taking the medicinal products containing the combination of ombitasvir/paritaprevir/ritonavir and dasabuvir as this may cause increases in liver function blood test results (increase in ALT liver enzyme). Use of Primolut N can be restarted approximately 2 weeks after completion of this treatment. See section" Do not use Primolut N ."
- **Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.**

Laboratory tests
If you are having a blood test, tell the doctor or laboratory personnel that you are using Primolut N since it may affect the results of some tests.

Primolut N with food and drink
Tablets are meant to be swallowed whole with liquid.

Pregnancy and breast-feeding
Do not use Primolut N if you are pregnant or suspect that you may be pregnant.
Do not use Primolut N if you are breast-feeding.
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
No studies have been conducted on how the product affects the ability to drive and use machines.

Primolut N contains lactose
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 Primolut N

Take the tablets whole with liquid .
If you have sexual intercourse, you should use non-hormonal contraception (e.g. condoms) instead of oral contraceptives. If you suspect that you have become pregnant despite using contraception ,stop using Primolut N until your doctor has examined you.
Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure .
The recommended dose is:

Bleeding disorders
Take 1 Primolut N tablet 3 times daily for 10 days. This will in most cases stop uterine bleeding with no associated organ damage within 1-3 days.

To achieve the therapeutic effect, Primolut N tablets must be taken regularly during the full 10-day treatment period even if bleeding stops before that.

About 2-4 days after the discontinuation of treatment, withdrawal bleeding will occur resembling normal menstruation in intensity and duration.

Occasionally slight bleeding may occur even after the initial arrest of bleeding. Do not stop or interrupt tablet taking even if this happens.

If the bleeding continues despite the fact that you have taken the tablets correctly, the possibility of an organic or extragenital cause should be considered. This kind of cause most often requires other treatment procedures. This also applies if heavy bleeding recurs after the arrest of bleeding during continued tablet taking.

- **Should this happen, contact your doctor.**

Your doctor may decide that you should take Primolut N preventively (in connection with an anovulatory cycle) to stop recurrence of bleeding disorders: 1 tablet 1-2 times daily from the 16^{th} to the 25^{th} day of the cycle (1^{st} day of cycle = 1^{st} day of bleeding). Withdrawal bleeding starts a few days after the medication is stopped.

Absence or stopping of menstruation (primary or secondary amenorrhea)
Hormone therapy can be used for absence of menstruation only when the possibility of pregnancy has been excluded. Sometimes the absence or stopping of menstruation is due to prolactinoma (lesions in the pituitary gland that produces increased amounts of hormone-like substances), and this possibility has to be excluded before starting therapy with Primolut N .

Your doctor will prescribe you estrogen (for 14 days, for example) before you start treatment with Primolut N. Thereafter take 1 Primolut N tablet 1-2 times daily for 10 days. Withdrawal bleeding starts a few days after the tablet taking is stopped.

If adequate estrogen production in the body has been achieved, administration of estrogen can be stopped and Primolut N can be used at a dosage of 1 tablet 2 times daily between the 16^{th} and 25^{th} day of the cycle in an attempt to induce cycle bleeding.

Premenstrual syndrome, mastopathy
Premenstrual symptoms such as headache, depressive moods, water retention and breast tenderness can be relieved at a dosage of 1 tablet 1-3 times daily during the progestational phase of the cycle.

Timing of menstruation
Primolut N tablets can be used to postpone menstruation but only in such cycles when there is no possibility of pregnancy.
Take 1 Primolut N tablet 2-3 times daily for no more than 10-14 days beginning about 3 days before the expected menstruation. Bleeding will start 2-3 days after the medication is stopped.

Endometriosis
Treatment is commenced between the 1st and 5th day of the cycle at a dosage of 1 Primolut N tablet twice daily. If spotting appears, the dose is increased to 2 tablets twice daily. If the bleeding ceases, the initial dosage can be resumed. The treatment is continued for at least 4-6 months. During the treatment, there will usually be no ovulation nor menstruation.
Withdrawal bleeding will start once the hormone treatment is stopped.

If you take more Primolut N than you should:
Do not take more Primolut N tablets than your doctor has prescribed.
There have been no reports of serious side effects from taking too many Primolut N tablets. If you have taken several tablets at one time, this may cause nausea, vomiting or vaginal bleeding. If you have taken a dose that is too high or if a child has taken the medicine by mistake, always contact your doctor or a hospital to assess the risk and receive further instructions .

If you forget to take Primolut N:
The effect of Primolut N may be reduced if you forget to take a tablet according to instructions. You should take only the last tablet you have forgotten as soon as possible and then continue with the tablet taking at the usual time the next day.
Do not take a double dose to make up for forgotten tablets.

If you stop taking Primolut N:
Stopping the use of Primolut N does not cause any specific symptoms but it is possible that the original symptoms will return.
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.
Side effects are more common during the first months of treatment and disappear gradually when the treatment is continued. In addition to the side effects mentioned in section» Warnings and precautions ,«the side effects listed below have been reported in connection with the use of Primolut N but their causal relationship with the product has not always been established. Here is a list of side effects according to their frequency:

Very common: 1 in 10 patients experience these:
- uterine bleeding / vaginal bleeding, including spotting *
- hypomenorrhea (scanty menstruation)*.

Common : 1-10 in 100 patients experience these:
- headache
- nausea
- absence of menstruation (amenorrhea)
- general water retention.

Uncommon: 1-10 in 1,000 patients experience these:
- migraine.

Rare: 1-10 patients in 10,000 experience these:
- hypersensitivity reactions
- hives
- rash
- breast tenderness, changes in libido.

Very rare :less than 1 in 10,000 patients experience these:
- disturbances in vision
- difficulty in breathing.

*In the endometriosis indication

Reporting of side effects:
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. By reporting side effects, you can help provide more information on the safety of this medicine.

5. HOW TO STORE Primolut N TABLETS

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 package. The expiry date refers to the last day of that month.
Do not store above 30°C.
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 Primolut N contains
- The active substance is norethisterone. Each Primolut N tablet contains 5 mg norethisterone.
- The other ingredients are: lactose monohydrate 70 mg, maize starch, magnesium stearate.

What Primolut N looks like and contents of the pack:
White, cross-scored tablets on one side with an emblem‘ AN ’in a hexagon on the other side.
30 tablets (2x15) in a blister pack (PVC/Aluminum).

Manufacturer
Bayer Weimar GmbH and Co. KG
99427 Weimar, Germany.

Marketing Authorization Holder:
Bayer AG
51373 Leverkusen, Germany.

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This is a medicament

- A medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

Keep medicament out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists