# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Primolut-Nor 5 mg tablets
Primolut-Nor 10 mg tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of Primolut-Nor 5 mg contains 5 mg of norethisterone acetate.
**Excipient with known effect**: 64 mg of lactose.

Each tablet of Primolut-Nor 10 mg contains 10 mg of norethisterone acetate.
**Excipient with known effect**: 59.26 mg of lactose.

For the full list of excipients, see section 6.1

## 3. PHARMACEUTICAL FORM

Tablet.

Primolut-Nor 5 mg: white tablet, cross-scored on one side and engraved on the other side with the letters “AP” inscribed in a regular hexagon.

Primolut-Nor 10 mg: white tablet, cross-scored on one side and engraved on the other side with the letters “AR” inscribed in a regular hexagon.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Secondary amenorrhoea and endometriosis.

### 4.2 Posology and method of administration

If contraceptive protection is required, non-hormonal methods of contraception must be used (barrier method).

Posology

Secondary amenorrhoea

Pregnancy must be excluded before the hormonal treatment of secondary amenorrhoea.

The presence of a prolactin-producing pituitary tumour should be excluded before starting the treatment of secondary amenorrhoea.

The endometrium must be prepared with an oestrogen (e.g. for 14 days) before starting treatment with 5 mg of norethisterone acetate. Thereafter 5 mg or 10 mg of norethisterone acetate should be administered daily for 10 days. Withdrawal bleeding will occur a few days after the last tablet is taken.

In patients in whom a sufficient production of endogenous oestrogen has been achieved, an attempt can be made to discontinue treatment and induce cycle bleeding by administering 5 mg of norethisterone acetate, twice daily, from the 16th to the 25th day of the cycle.

Endometriosis

Treatment must be started between the first and fifth day of the cycle with 5 mg of norethisterone acetate twice daily. If spotting appears, the dose can be increased to 10 mg of norethisterone acetate twice daily. If the bleeding stops, a reduction to the initial dose must be considered. Treatment must be continued for at least 4 to 6 months. With an uninterrupted daily intake, there is usually no ovulation or menstruation.

Method of administration
Oral use
The tablets must be swallowed whole with some liquid.

Posology

## 4.3 Contraindications

Primolut-Nor must not be used if any of the conditions mentioned below are present. This medicinal product must be discontinued immediately if any of these occurs during the use of Primolut-Nor:

- Pregnancy or suspected pregnancy
- Breast-feeding
- Presence or history of venous or arterial thrombotic/thromboembolic events (e.g. deep venous thrombosis, pulmonary embolism, myocardial infarction) or cerebrovascular accident.
- Presence or history of prodromes of a thrombosis (e.g. transient ischaemic attack, angina pectoris).
- High risk of venous or arterial thrombosis (see section 4.4).
- History of migraine with focal neurological symptoms.
- Diabetes mellitus with vascular complications.
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- Dubin-Johnson and Rotor syndrome, as well as jaundice or a history of severe pruritus in previous pregnancies.
- History of gestational pemphigoid (herpes gestationis).
- Presence or history of (benign or malignant) liver tumours.
- Known or suspected sex hormone-dependent malignancies (e.g. of the genital organs or breasts).
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Primolut-Nor is contraindicated for concomitant use with medicinal products that contain ombitasvir/paritaprevir/ritonavir and dasabuvir (see sections 4.4 and 4.5).

## 4.4 Special warnings and precautions for use

If any of the disorders or risks factors listed occurs or worsens, an individual risk-benefit assessment must be performed before treatment with Primolut-Nor is initiated or continued (see section 4.8).

- Vascular disorders

Epidemiological studies have shown that oral use of ovulation inhibitors containing oestrogens and progestins is associated with an increased incidence of thromboembolic diseases. The possibility of an increased thromboembolic risk should be kept in mind, especially if there is a history of this type of disease.

Generally recognised risk factors for venous thromboembolism (VTE) include positive personal or family history (VTE in a sibling or parent at a relatively young age), age, obesity, long-term immobilisation, major surgery or major trauma.

The increased risk of venous thromboembolism in the puerperium must be considered.

Treatment must be discontinued immediately if there are symptoms of a venous or arterial thrombotic event or suspicion thereof.

- Tumours

In rare cases benign, and in even rarer cases malignant, liver tumours have been reported in users of hormonal substances such as that contained in Primolut-Nor. In isolated cases these tumours have led to life-threatening intra-abdominal haemorrhages.

- Other conditions

Strict medical supervision is required in diabetic patients.

Chloasma may occasionally occur, especially in women with a history of chloasma of pregnancy. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking Primolut Nor.

Patients with a history of depression should be carefully monitored and the use of the drug must be stopped if the depression recurs in a more severe form.

- Medical examination/consultation

A complete medical history and medical and gynaecological examination should be taken prior to initiation or reinstitution of treatment with Primolut-Nor, guided by the contraindications (see section 4.3) and warnings (see section 4.4). These examinations should be repeated periodically during treatment with Primolut-Nor. The frequency and nature of these assessments should be adapted to the individual woman, but should generally include particular reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology.

- Reasons for discontinuing treatment immediately:

Occurrence for the first time of migrainous headache or increased frequency of exceptionally severe headache, sudden perceptual disorders, first signs of thrombophlebitis or thromboembolic symptoms, feeling of pain or tightness in the chest, scheduled surgery (six weeks prior), immobilization,

appearance of jaundice, appearance of anicteric hepatitis, generalised itching, significant increase in blood pressure, pregnancy.

Additional warnings relating to partial metabolism of norethisterone to ethinyloestradiol

Norethisterone is partly metabolised to ethinyloestradiol after oral administration, resulting in a dose equivalent to approximately 4–6 micrograms of ethinyloestradiol per milligram of norethisterone/norethisterone acetate administered orally.

Due to the partial conversion of norethisterone to ethinyloestradiol, the administration of Primolut-Nor is assumed to cause similar pharmacological effects to those observed with combined oral contraceptives (COCs). Therefore, the following general warnings associated with the use of COCs must be taken into account:

- Vascular disorders

The increased risk of VTE is highest during the first year that a woman starts using a COC for the first time or reinstates the use of COC after an interval of at least one month without taking any tablets.

Various epidemiological studies have shown that the incidence of VTE in users of combined oral contraceptives with a low oestrogen dose (< 50 micrograms ethinyloestradiol) ranges from 20 to 40 cases per 100,000 woman-years, but the risk estimate varies depending on the progestin. By comparison, the incidence is 5 to 10 cases per 100,000 woman-years in non-users. The use of all COCs is associated with an increased risk of VTE compared with non-use. This increased risk is smaller than the risk of VTE associated with pregnancy, estimated at 60 cases per 100,000 woman-years.

VTE may be life-threatening or fatal (in 1–2% of cases).

VTE, manifesting as deep venous thrombosis and/or pulmonary embolism, may occur during use of all COCs.

Extremely rarely, thrombosis has been reported to occur in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in COC users.

Symptoms of venous or arterial thrombotic/thromboembolic events or a cerebrovascular accident can include:

- unusual unilateral pain and/or inflammation of the lower limbs
- sudden severe pain in the chest, whether or not it radiates to the left arm
- sudden onset of an attack of breathlessness
- sudden onset of coughing episodes
- any unusual, severe, prolonged headache
- sudden, partial or complete loss of vision
- diplopia
- slurred speech or aphasia
- vertigo
- collapse with or without focal seizures
- weakness or very marked numbness suddenly affecting one side or one part of the body;
- motor disturbances
- acute abdomen

A possible increased synergistic risk of thrombosis must be considered in women with a combination of risk factors or with a single severe risk factor. The increase in risk may be greater than a simple

accumulation of risk due to these factors. A COC must not be prescribed if the risk/benefit assessment is negative (see section 4.3).

The risk of venous or arterial thrombotic / thromboembolic events or of a cerebrovascular accident increases with:

- age
- obesity (body mass index over 30 kg/m$^2$)
- positive family history (e.g. venous or arterial thromboembolism in a sibling or parent at a relatively early age). If a hereditary predisposition exists or is suspected, the woman should be referred to a specialist before deciding on the use of a COC
- prolonged immobilisation, major surgery, any surgery to the lower limbs or major trauma. In these situations it is advisable to stop taking the COC (in the case of elective surgery at least four weeks in advance) and not resume it until two weeks after complete remobilisation.
- smoking (the risk increases in heavy smokers and with age, especially in women over 35 years of age)
- dyslipoproteinaemia
- hypertension
- migraine
- valvular heart disease
- atrial fibrillation

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in the development of VTE.

Other conditions associated with adverse vascular events include diabetes mellitus, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell anaemia.

An increase in frequency or severity of migraine during COC use (which may be a prodrome of a cerebrovascular event) may be a reason for immediate discontinuation of COCs.

Biochemical factors that may be indicative of a hereditary or acquired predisposition for venous or arterial thrombosis include activated protein C (APC) resistance, hyperhomocysteinaemia, antithrombin III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (cardiolipin antibodies, lupus anticoagulant).

In the risk/benefit assessment, the physician should bear in mind that appropriate care may reduce the related risk of thrombosis and that the risk associated with pregnancy is greater than that associated with low-dose COCs (< 0.05 mg ethinyloestradiol).

- Tumours

The most important risk factor for cervical cancer is persistent human papilloma virus (HPV) infection.
An increased risk of cervical cancer in long-term users of combined oral contraceptives has been reported in some epidemiological studies, but there continues to be controversy about the extent to which this finding is attributable to related factors such as greater frequency of cervical screening, or sexual behaviour including use of barrier contraceptive methods.

A meta-analysis of 54 epidemiological studies showed that there is a slightly increased relative risk (RR = 1.24) of breast cancer being diagnosed in women who are currently using COCs. This risk gradually disappears in the 10 years following cessation of COC use. Since breast cancer is rare in

women under 40 years of age, the excess number of cases of breast cancer diagnosed in current and recent COC users is small in relation to the overall risk of breast cancer. These studies do not provide evidence for causality. The observed pattern of increased risk may be due to earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both factors. The breast cancers diagnosed in ever users of COCs tend to be less advanced clinically than the cancers diagnosed in never users.

Malignant tumours may be life-threatening or fatal.

- Other conditions

In women with hypertriglyceridaemia, or a family history thereof, the risk of developing pancreatitis may be increased during the use of COCs.

Although small increases in blood pressure have been reported in many women taking COCs, clinically significant increases are rare.

However, if sustained clinically significant hypertension develops in COC users, the physician is advised to exercise caution by withdrawing the COC and treating the hypertension. If considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.

The following conditions have been reported to occur or worsen with both pregnancy and COC use, but evidence of an association with COCs is inconclusive: jaundice and/or pruritus related to cholestasis, gallstones, porphyria, systemic lupus erythematosus haemolytic uraemic syndrome, Sydenham's chorea, herpes gestationis, otosclerosis-related hearing loss.

In women with hereditary angio-oedema, exogenous oestrogens may induce or exacerbate symptoms of angio-oedema.

Acute or chronic disturbances of liver function may necessitate the discontinuation of COC until liver function markers return to normal values. Discontinuation of COCs is necessary if cholestatic jaundice that has occurred previously during pregnancy or during the earlier use of sex hormones recurs.

Crohn's disease and ulcerative colitis have been associated with COC use.

- Increases in ALT

During clinical trials with patients treated for hepatitis C virus (HCV) infection with medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, increases in transaminases (ALT) of more than 5 times the upper limit of normal (ULN) have been observed significantly more often in women who were using medicinal products containing ethinyloestradiol, such as combined hormonal contraceptives (COCs). As norethisterone is metabolised partially to ethinyloestradiol, this warning applies to women who use norethisterone (see sections 4.3 and 4.5).

Warnings about excipients

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

## 4.5 Interaction with other medicinal products and other forms of interaction

N.B.: the summaries of product characteristics of the concomitant medicines must be consulted in order to identify interactions.

***Effects of other medicines on Primolut-Nor***
Interactions with drugs that induce microsomal enzymes may occur, which may result in increased clearance of sex hormones and which can lead to changes in the uterine bleeding profile and/or a reduction in the therapeutic effect.

Enzyme induction may occur after a few days of treatment. Peak enzyme induction is generally observed after a few weeks. When the medicinal therapy is discontinued, enzyme induction may persist for about 4 weeks.

*Substances that increase the clearance of sex hormones (reduction in efficacy due to enzyme induction), for example:*
Phenytoin, barbiturates, bosentan, primidone, carbamazepine, rifampicin and HIV medicines ritonavir, nevirapine and efavirenz, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products that contain St John's wort.

*Substances with variable effects on sex hormone clearance, for example:*
If co-administered with sex hormones, many combinations of HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors may increase or reduce plasma oestrogen or progesterone levels. These changes may be clinically relevant in some patients.

*Substances that reduce sex hormone clearance (enzyme inhibitors):*
The clinical relevance of the potential interactions with enzyme inhibitors is still unknown. Potent and moderate CYP3A4 inhibitors such as azole antifungals (e.g. itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice, may increase plasma levels of oestrogen or progesterone or both. Doses of etoricoxib of 60 to 120 mg/day have been observed to increase plasma levels of ethinyloestradiol by 1.4 to 1.6 times, respectively, if taken concomitantly with a combined hormone medicine containing 0.035 mg ethinyloestradiol.

***Effects of Primolut-Nor on other medicines***
Progestins may affect the metabolism of other drugs. Accordingly, their plasma and tissue concentrations may increase (e.g. ciclosporin) or decrease (e.g. lamotrigine). Clinical data suggest that ethinyloestradiol inhibits the elimination of CYP1A2 substrates, which leads to a slight (e.g. theophylline) or moderate (e.g. tizanidine) increase in plasma levels.

***Pharmacodynamic interactions***
Concomitant use with medicines that contain ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin, may increase the risk of an increase in ALT levels (see sections 4.3 and 4.4). Primolut-Nor may be reinstated 2 weeks after completing the treatment with this regimen of combined medicines.

***Other forms of interaction***
Interference with laboratory tests
Use of progestins may influence the results of certain laboratory tests.

**4.6 Fertility, pregnancy and lactation**

Primolut-Nor is contraindicated during pregnancy and lactation (see section 4.3).

**4.7 Effects on ability to drive and use machines**

Not known.

## 4.8 Undesirable effects

Adverse reactions are more common during the first months of administration of Primolut-Nor and abate over the course of treatment. The following adverse reactions have been reported in users of Primolut-Nor, although the causal relationship cannot always be confirmed.

The table below lists the adverse reactions by*MedDRA system organ classes* (MedDRA SOCs). The adverse reactions are listed in descending order of severity within each frequency range. The frequencies are based on post-marketing data and the relevant literature.

| System Organ Class (MedDRA) | Frequency of adverse reactions | | | | |
|---|---|---|---|---|---|
| | Very common (≥1/10) | Common (≥1/100 to <1/10) | Uncommon (≥1/1,000 to <1/100) | Rare (≥1/10,000 to <1/1,000) | Very rare (<1/10,000) |
| Immune system disorders | | | | Hypersensitivity reactions | |
| Nervous system disorders | | Headache | Migraine | | |
| Eye disorders | | | | | Visual disturbances |
| Respiratory, thoracic and mediastinal disorders | | | | | Dyspnoea |
| Gastrointestinal disorders | | Nausea | | | |
| Skin and subcutaneous tissue disorders | | | | Urticaria<br>Rash | |
| Reproductive system and breast disorders | Uterine/vaginal bleeding, including spotting*<br>Hypomenorrhoea* | Amenorrhoea* | | | |
| General disorders and administration site conditions | | Oedema | | | |

*in the indication endometriosis

The most appropriate MedDRA term is used to describe a given reaction, its synonyms and related conditions.

Frequency not known (cannot be estimated from the available data) (see section 4.4):
- thromboembolism
- hepatic tumours than cause intra-abdominal bleeding
- chloasma

- migrainous headaches or increased frequency of exceptionally severe headache, sudden perceptual disorders, first signs of thrombophlebitis or thromboembolic symptoms, feeling of pain or tightness in the chest, onset of jaundice, onset of anicteric hepatitis, generalised itching, significant increase in blood pressure.

Very high doses can occasionally cause cholestatic changes in the liver.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Spanish Pharmacovilance System for Medicinal Products for Human Use: www.notificaRAM.es

### 4.9 Overdose

Acute toxicity studies have not indicated a risk of acute adverse reactions in the event of inadvertent intake of a many times the therapeutic daily dose.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system; Progestogens: Estren derivatives.
ATC code: G03DC02

Norethisterone is a progestin. In women sensitised to oestrogens, complete transformation of the endometrium from the proliferative phase to the secretion phase can be achieved with oral norethisterone doses of 100–150 mg per cycle.

Secretion of gonadotropins and anovulation are suppressed with a daily 0.5-mg dose of norethisterone acetate.

Norethisterone is thermogenic and alters the basal body temperature.

### 5.2 Pharmacokinetic properties

- Absorption

During absorption and the hepatic first pass, norethisterone acetate (NETA) is hydrolysed to the active pharmaceutical ingredient of the medicinal product, norethisterone, and acetic acid. Peak plasma levels of norethisterone of 18 ng/ml (after a 5-mg dose of NETA) and 25 ng/ml (after a 10-mg dose of NETA) are reached about 2 hours after administration of a Primolut-Nor tablet. According to a relative bioavailability study, the drug is completely released from the tablet.

- Distribution

Norethisterone is bound to plasma albumin and sex hormone-binding globulin (SHBG). Only about 3-4% of the total drug content in plasma is recovered as unbound steroid, about 35% is bound to SHBG and 61% to albumin. The apparent distribution volume of norethisterone is 4.4 ± 1.3 l/kg. After oral

administration, the time curve of the plasma drug levels follows a biphasic pattern. The plasma half-life characteristic of each of these phases is 1–3 hours and between 5 and 13 hours, respectively.

Steady-state conditions:
During daily administration of multiple doses of norethisterone, accumulation of the drug is unlikely due to its relatively short half-life. However, if SHBG-inducing substances such as ethinyloestradiol are administered concurrently, an increase in plasma levels of norethisterone can occur as a result of its binding to SHBG.

- Metabolism

Norethisterone is metabolised predominantly by saturation of the A-ring double bond and reduction of a 3-keto group to a hydroxyl group, followed by conjugation with corresponding sulphates and glucuronides. Some of these metabolites are eliminated very slowly from plasma, with plasma half-lives of about 67 hours. Therefore, during prolonged treatment with daily oral norethisterone, some of the metabolites mentioned will accumulate in plasma.

Norethisterone is metabolised partly into ethinyloestradiol in humans after oral administration of norethisterone acetate. This conversion leads to a dose equivalent to approximately 4-6 micrograms of ethinyloestradiol per milligram of orally administered norethisterone/norethisterone acetate.

- Elimination

No significant amounts of unchanged norethisterone are excreted. Predominantly A-ring-reduced and hydroxylated metabolites, as well as their conjugates (glucuronides and sulphates), are excreted in urine and faeces in a ratio of 7:3. The majority of renally excreted metabolites are eliminated within 24 hours with a plasma half-life of about 19 hours.
Norethisterone is excreted in breast milk and drug levels in milk are about 10% of the levels in the mother's plasma, regardless of the route of administration. If the average drug peak levels in the mother's plasma are assumed to be about 16 ng/ml and the child is estimated to receive about 600 ml of milk each day, about 1 microgram of the drug (0.02% of the mother's dose) can pass into the child.

### 5.3 Preclinical safety data

Preclinical data for norethisterone and its esters reveal no special hazard for humans based on conventional studies of safety, repeated dose toxicity, genotoxicity and carcinogenicity. However, it should be kept in mind that sex steroids may stimulate the growth of hormone-dependent tissues and tumours.

Reprotoxicity studies show the risk of virilisation of female fetuses when high doses are administered at the time of development of the external genitalia.

In addition, epidemiological studies have shown that this effect is relevant in humans after the administration of high doses.

Primolut-Nor may induce signs of virilisation in female fetuses if administered during the hormone-sensitive stage of somatic sexual differentiation (from day 45 of pregnancy onwards). Apart from those mentioned, no other indications of teratogenic effects were obtained in the studies.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Lactose monohydrate
Maize starch
Povidone 25000
Talc
Magnesium stearate

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

5 years.

### 6.4 Special precautions for storage

Store in the original packaging to protect from light.

### 6.5 Nature and contents of container

Primolut-Nor tablets are contained in blister packs composed of transparent polyvinyl chloride film and aluminium metal foil (heat-sealable).

Pack sizes:

Primolut-Nor 5 mg: blister pack of 20 tablets.
Primolut-Nor 5 mg: blister pack of 30 tablets.
Primolut-Nor 10 mg: blister pack of 30 tablets.

### 6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

Bayer Hispania, S.L.
Av. Baix Llobregat, 3 - 5
08970 Sant Joan Despí – Barcelona
Spain

## 8. MARKETING AUTHORISATION NUMBERS

Primolut-Nor 5 mg: 39.927
Primolut-Nor 10 mg: 44.646

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Primolut-Nor 5:
Date of first authorisation 23.07.1964
Date of latest renewal 16.06.2012
Primolut-Nor 10:
Date of first authorisation 16.06.1967
Date of latest renewal 16.06.2012

## 10. DATE OF REVISION OF THE TEXT

04/2019

Detailed information on this medicinal product is available on the website of The Spanish Agency of Medicines and Medical Devices (AEMPS) http://www.aemps.gob.es