Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Primolut N 5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5mg norethisterone.

Excipients: also includes Lactose Monohydrate 70.0mg per tablet.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet.

Round, white, flat 7 mm tablet, impressed with 'AN' in a regular hexagon on one side

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Dysfunctional bleeding, endometriosis

4.2 Posology and method of administration

Posology
The tablets are to be swallowed whole with some liquid.

The efficacy of Primolut N could be reduced if the user forgets to take a tablet as directed. The woman should take only the last missed tablet as soon as she remembers and then continue tablet intake at her usual time on the next day.

If contraceptive protection is required, additional non-hormonal, barrier contraceptive methods should be used.

Dysfunctional bleeding
Primolut N 1 tablet is to be taken 3 times daily for 10 days. In the majority of cases this will arrest uterine bleeding that is not associated with organic lesions within 1 to 3 days, nevertheless to ensure treatment success Primolut N must be taken for the full 10 days. About 2 to 4 days after completion of the treatment, withdrawal bleeding will occur with the intensity and duration of normal menstruation.

Slight bleeding during tablet taking
Occasionally, slight bleeding may occur after the initial suspension of bleeding. Also in these cases tablet intake should not be interrupted or stopped.

Missing arrest of haemorrhage, heavy breakthrough bleeding
If vaginal bleeding does not stop, despite correct tablet intake, an organic cause or an extra-genital factor (e.g. polyps, carcinoma of the cervix uteri or endometrium, myoma, residua of abortion, extra-uterine pregnancy or coagulation disorders) must be considered so that other measures are then mostly required. This also applies to cases where after an initial suspension of bleeding, fairly heavy bleeding reoccurs during tablet intake.

Prevention of recurrence
To prevent dysfunctional bleeding recurrence in patients with anovulatory cycles Primolut N can be administered prophylactically (1 tablet 1 to 2 times daily from the 16th to the 25th day of the cycle. 1st day of the cycle = 1st day of the last bleeding). Withdrawal bleeding occurs a few days after the last tablet intake.

Endometriosis
Treatment should begin between the first and 5th day of the cycle with 1 tablet Primolut N twice daily. In the event of spotting, the dose can be increased to 2 tablets twice daily. If bleeding ceases, dose reduction to the initial dose should be considered. Treatment is to be continued for at least 4 to 6 months. With uninterrupted daily intake, ovulation and menstruation do not usually occur. After discontinuation of hormone treatment withdrawal bleeding will occur.

Method of Administration
Oral use

4.3 Contraindications

Primolut N should not be used in the presence of any of the conditions listed below, which are derived also from information on progestogen-only products and combined oral contraceptives (COCs). Should any of the conditions appear during the use of Primolut N, use of the product should be stopped immediately.

- Known or suspected pregnancy
- Lactation
- Presence or a history of venous or arterial thrombotic/thromboembolic events (e.g. deep venous thrombosis, pulmonary embolism, myocardial infarction) or of a cerebrovascular accident
- Presence or a history of prodromi of a thrombosis (e.g. transient ischaemic attack, angina pectoris).
- A high risk of venous or arterial thrombosis (see 'Special warnings and precautions for use')
- History of migraine with focal neurological symptoms.
- Diabetes mellitus with vascular involvement
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal
- Presence or history of liver tumours (benign or malignant)
- Known or suspected sex hormone-dependent malignancies (e.g. of the genital organs or the breasts)
- Hypersensitivity to the active substances or to any of the excipients
- Undiagnosed irregular vaginal bleeding

Primolut N is contraindicated for concomitant use with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir (see section 4.4 and 4.5).

4.4 Special warnings and precautions for use

If any of the conditions/risk factors mentioned below is present or deteriorates, an individual risk-benefit analysis should be done before Primolut N is started or continued.

Circulatory disorders
It has been concluded from epidemiological surveys that the use of oral oestrogen/progestogen containing ovulation inhibitors is attended by an increased incidence of thromboembolic diseases. Therefore, one should keep the possibility of an increased thromboembolic risk in mind, particularly where there is a history of thromboembolic diseases.

Generally recognized risk factors for venous thromboembolism (VTE) include a positive personal or family history (VTE in a sibling or a parent at a relatively early age), age, obesity, prolonged immobilization, major surgery or major trauma.

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

Treatment should be stopped at once if there are symptoms of an arterial or venous thrombotic event or suspicion thereof.

Tumours
In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of hormonal substances such as the one contained in Primolut N. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. A hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking Primolut N.

Other

Strict medical supervision is necessary if the patient suffers from diabetes.

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation when taking Primolut N.

Patients who have a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

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

Medical examination
A complete medical history should be taken and a physical and gynaecological examination should be performed prior to the initiation or reinstitution of the use of Primolut N, guided by the contraindications (Section 4.3) and warnings (Section 4.4), and these should be repeated during the use of Primolut N. The frequency and nature of these assessments should be adapted to the individual woman but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs, and should also include cervical cytology.

Reasons for immediate discontinuation of the tablets are:
Occurrence for the first time of migrainous headaches or more frequent occurrence of unusually severe headaches, sudden perceptual disorders (e.g. disturbances of vision or hearing), first signs of thrombophlebitis or thromboembolic symptoms (for example, unusual pains in or swelling of the legs, stabbing pains on breathing or coughing for no apparent reason), a feeling of pain and tightness in the chest, pending operations (six weeks beforehand), immobilisation (for instance, following accidents), onset of jaundice, onset of anicteric hepatitis, generalised pruritus, significant rise in blood pressure, pregnancy.

4.4.1 Additional warnings based on the partial metabolization of norethisterone to ethinylestradiol
After oral administration, norethisterone is partly metabolized to ethinylestradiol resulting in an equivalent dose of about 4-6 µg ethinylestradiol per 1 mg orally administered norethisterone / norethisterone acetate (see 'Pharmacokinetic properties').

Due to the partial conversion of norethisterone to ethinylestradiol, administration of Primolut N is expected to result in similar pharmacological effects as seen with COCs. Therefore the following general warnings associated with the use of COCs should be considered in addition:

Circulatory disorders
The risk of VTE is highest during the first year of use. This increased risk is present after initially starting a COC or restarting (following a 4 week or greater pill free interval) the same or a different COC. Data from a large, prospective 3-armed cohort study suggest that this increased risk is mainly present during the first 3 months.
Overall the risk for venous thromboembolism (VTE) in users of low estrogen dose (< 50 µg ethinylestradiol) COCs is two to threefold higher than for non-users of COCs who are not pregnant and remains lower than the risk associated with pregnancy and delivery.
VTE may be life-threatening or may have a fatal outcome (in 1-2 % of the cases).
Venous thromboembolism (VTE), manifesting as deep venous thrombosis and/or pulmonary embolism, may occur during the 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 deep venous thrombosis (DVT) can include: unilateral swelling of the leg or along a vein in the leg; pain or tenderness in the leg which may be felt only when standing or walking, increased warmth in the affected leg; red or discolored skin on the leg.
Symptoms of pulmonary embolism (PE) can include: sudden onset of unexplained shortness of breath or rapid breathing; sudden coughing which may bring up blood; sharp chest pain, which may increase with deep breathing; sense of anxiety; severe light headedness or dizziness; rapid or irregular heartbeat. Some of these symptoms (e.g. "shortness of breath", "coughing") are non-specific and might be misinterpreted as more common or less severe events (e.g. respiratory tract infections).
An arterial thromboembolic event can include cerebrovascular accident, vascular occlusion or myocardial infarction (MI).
Symptoms of a cerebrovascular accident can include: sudden numbness or weakness of the face, arm or leg, especially on one side of the body; sudden confusion, trouble speaking or understanding; sudden trouble seeing in one or both eyes; sudden trouble walking, dizziness, loss of balance or coordination; sudden, severe or prolonged headache with no known cause; loss of consciousness or fainting with or without seizure. Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discoloration of an extremity; acute abdomen.

Symptoms of MI can include: pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm, or below the breastbone; discomfort radiating to the back, jaw, throat, arm, stomach; fullness, indigestion or choking feeling; sweating, nausea, vomiting or dizziness; extreme weakness, anxiety, or shortness of breath; rapid or irregular heartbeats.
Arterial thromboembolic events may be life-threatening or may have a fatal outcome.
The potential for an increased synergistic risk of thrombosis should be considered in women who possess a combination of risk factors or exhibit a greater severity of an individual risk factor. This increased risk may be greater than a simple cumulative risk of the factors. A COC should not be prescribed in case of a negative risk benefit assessment (see section 'Contraindications').
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)
- A positive family history (i.e. venous or arterial thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is known or suspected, the woman should be referred to a specialist for advice before deciding about any COC use
- Prolonged immobilization, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue COC use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilization
- Smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age)
- Dyslipoproteinemia
- Hypertension
- Migraine
- Valvular heart disease
- Atrial fibrillation

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in venous thromboembolism.
Other medical conditions which have been associated with adverse circulatory events include diabetes mellitus, systemic lupus erythematosus, hemolytic uremic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.
An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.
Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C (APC) resistance, hyperhomocysteinemia, antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).
When considering risk/benefit, the physician should take into account that adequate treatment of a condition may reduce the associated risk of thrombosis and that the risk associated with pregnancy is higher than that associated with low-dose COCs (<0.05 mg ethinylestradiol).

Tumors
The most important risk factor for cervical cancer is persistent HPV infection. Some epidemiological studies have indicated that long-term use of COCs may further contribute to this increased risk but there continues to be controversy about the extent to which this finding is attributable to confounding effects, e.g., cervical screening and sexual behaviour including use of barrier contraceptives.
A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.
Malignancies may be life-threatening or may have a fatal outcome.

Other conditions
Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.
Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare.
However, if a sustained clinically significant hypertension develops during the use of a COC then it is prudent for the physician to withdraw the COC and treat the hypertension. Where 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 deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria;

systemic lupus erythematosus; hemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.
In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.
Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal. Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of COCs.
Crohn's disease and ulcerative colitis have been associated with COC use.

ALT elevations
During clinical trials with patients treated for hepatitis C virus infections (HCV) with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequent in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs). As norethisterone is partly metabolized into ethinylestradiol, this warning applies to women using norethisterone (see sections 4.3 and 4.5).

4.5 Interaction with other medicinal products and other forms of interactions

Effects of other medicinal products on Primolut N

Interactions can occur with drugs that induce microsomal enzymes, which can result in an increased clearance of sex hormones, and which may lead to changes in the uterine bleeding profile and/or reduction of the therapeutic effect.

Enzyme induction can already be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After the cessation of drug therapy enzyme induction may be sustained for about 4 weeks.

Substances increasing the clearance of sex hormones (diminished efficacy by enzyme-induction), e.g.:

Phenytoin, barbiturates, bosentan, primidone, carbamazepine, rifampicin and HIV medication ritonavir, nevirapine and efavirenz, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St. John's wort.

Substances with variable effects on the clearance of sex hormones, e.g.:

When co-administered with sex hormones, many HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of estrogen or progestin. These changes may be clinically relevant in some cases.

Substances decreasing the clearance of sex hormones (enzyme inhibitors):
The clinical relevance of potential interactions with enzyme inhibitors remains unknown.
Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of the estrogen or the progestin or both.
Etoricoxib doses of 60 to 120 mg/day have been shown to increase plasma concentrations of ethinylestradiol 1.4 to 1.6-fold, respectively when taken concomitantly with a combined hormonal medicinal product containing 0.035 mg ethinylestradiol.

Effects of Primolut N on other medicinal products

Progestogens may interfere with the metabolism of other drugs. Accordingly, plasma and tissue concentrations may either increase (e.g. cyclosporin) or decrease (e.g. lamotrigine).Clinical data suggest that ethinylestradiol inhibits the clearance of CYP1A2 substrates, leading to a weak (e.g. theophylline) or moderate (e.g. tizanidine) increase in plasma concentration.

Note: the prescribing information of concomitant medications should be consulted to identify potential interactions.

Pharmacodynamic interactions

Concomitant use with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin may increase the risk of ALT elevations (see sections 4.3 and 4.4). Primolut N can be restarted 2 weeks following completion of treatment with this combination drug regimen.

Other forms of interaction

Laboratory tests

The use of progestogens may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins, e.g. corticosteroid binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

4.6 Fertility, pregnancy and lactation

The use of Primolut N during pregnancy is contraindicated.

Primolut N should not be used during lactation

4.7 Effects on ability to drive and use machines

Not known

4.8 Undesirable effects

Undesirable effects are more common during the first months after start of intake of Primolut preparations and subside with duration of treatment. In addition to the undesirable effects listed in *section 4.4, Special Warnings and precautions for use*, the following undesirable effects have been reported in users of Primolut preparations although a causal relationship could not always be confirmed:

The table below reports adverse reactions by MedDRA system organ classes (MedDRA SOCs). The frequencies are based on reporting rates from postmarketing experience and literature.

System organ class (MEDRA)	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1,000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1000)**	**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 Rash	
Reproductive system and breast disorders	Uterine/Vaginal bleeding including Spotting* Hypomenorrhoea*	Amenorrhoea*			
General disorders and administration site conditions		Oedema			

*in the indication “endometriosis”.

The most appropriate MedDRA term is used to describe a certain reaction and it's synonyms and related conditions.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Acute toxicity studies in animals performed with norethisterone acetate did not indicate a risk of acute adverse effects in case of inadvertent intake of a multiple of the daily therapeutic 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 strong progestogen. Complete transformation of the endometrium from a proliferative to a secretory state can be achieved in oestrogen-primed women with orally administered doses of 100-150 mg norethisterone per cycle. The progestogenic effects of norethisterone on the endometrium are the basis of the treatment of dysfunctional bleeding and endometriosis with Primolut N.

Gonadotropin secretion inhibition and anovulation can be achieved with a daily intake of 0.5 mg of norethisterone. Positive effects of Primolut N on premenstrual symptoms can be traced back to suppression of ovarian function.

Like progesterone, norethisterone is thermogenic and alters the basal body temperature.

5.2 Pharmacokinetic properties

Absorption
Orally administered norethisterone is rapidly and completely absorbed over a wide dose range.
Peak serum concentrations of about 16 ng/ml are reached within about 1.5 hours of administration of one tablet Primolut N.
Due to a marked first-pass effect, the bioavailability of norethisterone after an oral dose is about 64%.

Distribution
Norethisterone is bound to serum albumin and to sex hormone binding globulin (SHBG). Only about 3-4% of the total serum drug concentrations are present as free steroid. About 35% and 61% are bound to SHBG and albumin, respectively. The apparent volume of distribution of norethisterone is 4.4 ± 1.3 l/kg. Following oral administration, the drug serum level time course follows a biphasic pattern. Both phases are characterized by half-lives of 1-2 and about 5-13 hours, respectively.

Norethisterone is transferred into milk and the drug levels in breast milk were found to be about 10% of those found in maternal plasma, irrespective of the route of administration. Based on a mean maximum drug level in maternal serum of about 16 ng/ml and an estimated daily intake of 600 ml of milk by the nursed infant, a maximum of about 1 µg (0.02% of the maternal dose) could reach the infant.

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

Norethisterone is partly metabolized to ethinylestradiol after oral administration of norethisterone or norethisterone acetate in humans. This conversion results in an equivalent dose of about 4-6 ug ethinylestradiol per 1 mg orally administered norethisterone / norethisterone acetate.

Elimination
Norethisterone is not excreted unchanged to a significant extent. Predominantly A-ring-reduced and hydroxylated metabolites as well as their conjugates (glucuronides and sulphates) are excreted via urine and faeces in a ratio of about 7:3. The bulk of renally excreted metabolites was eliminated within 24 hours with a half-life of about 19 hours.

Steady-state conditions
During multiple-dose daily administration with norethisterone, an accumulation of the drug is unlikely because of the relatively short half-life of the drug. If, however, SHBG-inducing agents such as ethinylestradiol are co-administered, an increase in norethisterone serum levels can occur because of the binding of norethisterone to SHBG.

5.3 Preclinical safety data

Non-clinical data on norethisterone or its esters reveal no special risk for humans based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenic potential which is not already included in other relevant sections. However, it should be kept in mind that sexual steroids might stimulate the growth of hormone-dependent tissues and tumours.

Reproduction toxicity studies showed a risk of masculinization in female foetuses when administered at high doses at the time of the development of the external genitalia. Since epidemiological studies show that this effect is relevant in humans after high doses, it must be stated that Primolut N may provoke signs of virilization in female foetuses if administered during the hormone-sensitive stage of somatic sexual differentiation (from day 45 of pregnancy onwards). Apart from this, no indications of teratogenic effects were obtained from the studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate
Maize Starch
Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store below 25^{o}C.

6.5 Nature and contents of container

Glass bottles of 100 tablets.

Pack of 20 or 30 tablets of 5mg each sealed in deep-drawn strips made of polyvinyl chloride film with counter sealing foil made of aluminium with heat sealable coating.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Bayer Limited
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Blackthorn Road
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8 MARKETING AUTHORISATION NUMBER

PA1410/010/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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