Bayer

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Primolut Nor 10 mg tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
One tablet contains:
Active Substance: norethisterone acetate 10 mg.
Excipients: lactose 62.375 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Tablet

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Dysfunctional bleeding, primary and secondary amenorrhea, premenstrual syndrome, mastopathy, timing of menstruation, endometriosis.

4.2 Posology and method of administration

Methods of administration
Oral use

Posology

The tablets must be swallowed with a little liquid.
The efficacy of Primolut Nor may be reduced if the tablets are not all taken in accordance with the instructions. A woman must take only the last missed tablet as soon as she remembers and then continue with tablet-taking at the usual time the next day.

If contraceptive protection is necessary, the use of additional non-hormonal (barrier) contraceptive methods is recommended.

- **Functional metrorrhagia**

Taking half a Primolut Nor tablet (= 5 mg) three times daily for 10 days leads to cessation of uterine bleeding not associated with organic lesions within 1-3 days in most cases. Nevertheless, in order to ensure that the treatment is completely successful, it is necessary to take Primolut Nor regularly for the full 10-day period.
Approximately 2-4 days after completion of the treatment, a withdrawal bleed occurs resembling a normal period in terms of intensity and duration.

Slight bleeding during tablet-taking
Occasionally, slight bleeding may occur after the initial cessation of bleeding. Even in these cases, tablet-taking must not be interrupted or discontinued.

No cessation of bleeding, heavy breakthrough bleeding
If the bleeding does not stop despite the tablets being taken as directed, an organic cause or an extra-genital factor (e.g. polyps, cervical or endometrial cancer, fibroids, abortion residua, ectopic pregnancy or coagulation disorders) must be considered, for which other therapeutic measures are generally required. The same applies where, after initial cessation of bleeding, fairly heavy bleeding reappears during tablet-taking.

Prevention of recurrence
To prevent recurrences in patients with anovulatory cycles, Primolut Nor may be taken prophylactically (1/2 tablet - 5 mg - 1-2 times daily from Days 16 to 25 of the cycle (Day 1 of the cycle = 1st day of the last period)). Withdrawal bleeding will occur a few days after the last tablet is taken.

- **Primary and secondary amenorrhoea**

Hormone treatment of secondary amenorrhoea must be started only after pregnancy has been ruled out.
Before the start of treatment of primary or secondary amenorrhoea, the presence of a prolactin-producing pituitary tumour must be ruled out. This is because any macroadenomas exposed to high levels of oestrogens for prolonged periods of time may increase in size.
Before treatment with Primolut Nor is started, pretreatment of the endometrium with an oestrogen is required (e.g. for 14 days). Half a Primolut Nor 10 mg tablet (= 5 mg) should then be taken 1-2 times daily for 10 days. Withdrawal bleeding will occur a few days after the last tablet is taken.
In patients in whom sufficient endogenous oestrogen production has been attained, an attempt can be made to discontinue the treatment with oestrogens and to induce cyclical bleeding by administering half a Primolut Nor 10 mg tablet twice daily from Days 16 to 25 of the cycle.

- **Premenstrual syndrome, mastopathy**

Half a Primolut Nor 10 mg tablet 1-3 times daily during the luteal phase of the cycle may alleviate or improve premenstrual symptoms such as headache, depressed mood, fluid retention and breast tenderness.

- **Timing of menstruation**

Primolut Nor tablets can be used to postpone menstruation but only in such cycles when there is no possibility of pregnancy.
Dosage: half a Primolut Nor 10 mg tablet (= 5 mg) 2-3 times daily for no more than 10-14 days, starting approximately 3 days before the estimated date of menstruation. Menstruation will occur 2-3 days after discontinuation of treatment.

- **Endometriosis**

Treatment must start between Days 1 and 5 of the cycle with half a Primolut Nor 10 mg tablet (= 5 mg) twice daily, with the dose being increased if necessary to one tablet per day in the presence of spotting. If this disappears, the initial dosage may be resumed. Treatment must be continued for at least 4-6 months. If the medicinal product is taken each day without interruption, ovulation and menstruation will not usually occur. After discontinuation of the hormone treatment, withdrawal bleeding will occur.

4.3 Contraindications

Primolut Nor must not be used in the presence of the conditions listed below, which are derived partly from information on progestogen-only products and combined oral contraceptives (COCs). Should any of these conditions appear during the use of Primolut Nor, the treatment must be discontinued immediately.

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- verified or presumed pregnancy
- lactation
- presence or history of venous or arterial thrombosis/thromboembolic events (e.g. deep vein thrombosis, pulmonary embolism, myocardial infarction) or cerebrovascular accidents
- presence or history of thrombosis prodromes (e.g. transient ischaemic attack, angina pectoris)
- major risk factor for venous or arterial thrombosis (see section "Special warnings and precautions for use")
- history of migraine accompanied by focal neurological symptoms
- diabetes mellitus with vascular involvement
- presence or history of severe liver disease until liver function values have returned to normal

- presence or history of (benign or malignant) liver tumours
- verified or suspected sex hormone-dependent malignancies (e.g. of the genital organs or of the breast)

The concomitant use of Primolut Nor with medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir is contraindicated (see sections 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 analysis of the risk-benefit relationship must be carried out before the start or continuation of treatment with Primolut Nor.

- **Circulatory disorders**

It has been concluded from the results of epidemiological studies that the use of oestrogen-/progestogen-containing ovulation inhibitors is associated with an increased incidence of thromboembolic diseases. The possibility of an increased risk of thromboembolism should therefore be borne in mind, particularly in the presence of a history of thromboembolic disease.

The generally recognised risk factors for venous thromboembolism (VTE) include a positive personal or family history (presence of VTE in a sibling or parent at a relatively early age), age, obesity, prolonged immobilisation, major surgery or major trauma.

The increased risk of thromboembolism during the postpartum period must be taken into consideration.

Treatment must be discontinued immediately if symptoms of arterial or venous thrombosis appear or if such conditions are suspected.

- **Tumours**

In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in women taking hormonal substances such as the one contained in Primolut Nor. In isolated cases, these tumours have led to the patient suffering from life-threatening intra-abdominal bleeding.

If a woman taking Primolut Nor experiences severe upper abdominal pain, liver enlargement or signs of intra-abdominal bleeding, a liver tumour must be taken into consideration in the differential diagnosis.

- **Other conditions**

In diabetic subjects, particular caution must be exercised by the physician.

Chloasma may develop occasionally, particularly in women with a history of chloasma gravidarum. Women with a tendency to chloasma must avoid exposure to the sun or ultraviolet radiation during use of Primolut Nor.

Patients with a history of mental depression should be kept under close observation, and administration of the medicinal product discontinued if the depression recurs in a severe form.

- **Medical examination**

Prior to the start or resumption of Primolut Nor use, a complete history must be taken and a physical and gynaecological examination performed, taking into account the contraindications (see

section 4.3) and the warnings (see section 4.4), to be repeated periodically during treatment. The frequency and nature of the checks must be tailored to the individual patient, but must generally pay particular attention to arterial blood pressure, the breasts, abdomen and pelvic organs, including cervical cytology.

- **Reasons for immediate discontinuation of treatment are:**

First-time occurrence of migraine headaches or increased frequency of unusually severe headaches, sudden disorders of perception (e.g. visual or hearing impairment), first signs of thrombophlebitis or thromboembolic symptoms (e.g. unusual leg pain or swelling, sharp pain when breathing or coughing for no apparent reason), a feeling of pain or tightness in the chest, elective surgery (six weeks beforehand), immobilisation (e.g. following accidents), development of jaundice or hepatitis without jaundice, generalised pruritus, significant rise in arterial blood pressure, pregnancy.
In the event of endocrine and liver function test abnormalities, treatment should be discontinued and the tests repeated after approximately 2 months.

- **Information relating to the excipients**

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

- **Partial metabolism of norethisterone to ethinylestradiol**

After oral administration, norethisterone is partially metabolised to ethinylestradiol; a dose equivalent to approximately 4-6 micrograms ethinylestradiol corresponds to 1 milligram norethisterone (see "Pharmacokinetic properties").

Following the partial transformation of norethisterone to ethinylestradiol, administration of Primolut Nor is expected to result in similar pharmacological effects to those observed with COCs. The following general warnings associated with COC use must therefore also be taken into consideration:

Circulatory disorders

The additional risk of VTE is higher during the first year of use when a woman is using a COC for the first time or when a woman is resuming COC use after a pill-free interval of at least one month.

Epidemiological studies have shown that the incidence of venous thromboembolism (VTE) in women using COCs with a low oestrogen content (<50 micrograms ethinylestradiol) ranges from approximately 20 to 40 cases per 100,000 woman-years, but this risk estimate varies depending on the progestogen component. This compares with 5-10 cases per 100,000 woman-years for non-users. The use of any combined oral contraceptive (COC) carries an increased risk of venous thromboembolism (VTE) compared with non-use. This increased risk is nevertheless lower than the risk of VTE associated with pregnancy, which is estimated at 60 cases per 100,000 pregnancies.

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

Venous thromboembolism (VTE) manifesting as deep vein thrombosis and/or pulmonary embolism may occur during use of all COCs.

Very rarely, thrombosis has been reported to occur in other vascular territories in COC users, e.g. hepatic, mesenteric, cerebral, renal or retinal veins and arteries.
The symptoms of venous or arterial thrombotic/thromboembolic events or of a cerebrovascular accident may include:

- unusual unilateral pain and/or swelling in a leg
- severe and sudden chest pain, with or without radiation to the left arm
- sudden dyspnoea
- sudden onset of cough
- unusual, severe and prolonged headache
- sudden partial or complete loss of vision
- diplopia
- unclear speech or aphasia
- vertigo
- collapse with or without focal seizures
- sudden weakness or very marked numbness affecting one side or one part of the body
- motor disturbances
- "acute" abdomen

The possibility of an increased synergistic risk of thrombosis must be taken into consideration in women with a combination of risk factors or who exhibit an individual risk factor of greater severity. This increased risk may be greater than a simple cumulative risk of the factors. In the event of a negative risk/benefit assessment, a COC must not be prescribed (see section "Contraindications").

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

- age
- obesity (body mass index greater than 30 kg/m²)
- a positive family history (arterial or venous thromboembolism in a sibling or parent at a relatively young age). If a hereditary predisposition is suspected, a woman must consult a specialist for an opinion before deciding to take any COC
- prolonged immobilisation, major surgery, any surgery to the legs or major trauma. In these circumstances, it is advisable to discontinue COC administration (in the case of elective surgery at least 4 weeks in advance) and not to resume it until 2 weeks after complete remobilisation
- smoking (the risk increases further for heavy smokers and with increasing age, especially for women over 35 years of age)
- dyslipoproteinaemia
- hypertension
- migraine
- valvular heart disease
- atrial fibrillation

There is no consensus regarding the possible role of varicose veins and superficial thrombophlebitis in venous thromboembolism.

Other medical conditions that have been 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 disease.

An increase in the frequency and severity of migraine during COC use (which may be an early sign of a cerebrovascular event) may represent a reason for immediate discontinuation of the COC.

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

When considering the risk-benefit relationship, the physician must bear in mind that adequate treatment of a clinical condition may reduce the associated risk of thrombosis and that the risk associated with pregnancy is higher than that associated with the use of low-dose combined oral contraceptives (<50 micrograms ethinylestradiol).

Tumours
The most important risk factor for cervical cancer is human papillomavirus (HPV) infection. Some epidemiological studies have indicated an increase in the risk of cervical cancer in long-term users of COCs, but there is still controversy regarding the extent to which this finding is attributable to confounding effects attributable to cervical screening and to sexual behaviour, including the use of barrier contraceptive methods.

A meta-analysis of 54 epidemiological studies showed that women currently using COCs have a slightly increased relative risk (RR=1.24) of being diagnosed with breast cancer. The excess risk gradually disappears during the course of the 10 years after discontinuation of COCs. Because breast cancer is rare in women under 40 years of age, the excess number of cases of breast cancer in current or recent COC users is small in relation to the overall risk of breast cancer. These studies do not provide any proof of a causal relationship. The increase in risk observed may be due to earlier diagnosis of breast cancer in women using COCs, to the biological effects of COCs or to a combination of the two factors. Breast cancer diagnosed in COC users tends to be clinically less advanced compared with that diagnosed in never-users.

Malignancies may be life-threatening or may be fatal.

Other conditions

Women with hypertriglyceridaemia or with a family history of this condition may find themselves at increased risk of pancreatitis when they use COCs.

Although a slight increase in blood pressure has been found in many women taking combined oral contraceptives, a clinically relevant increase is a rare event.

Nevertheless, if clinically significant hypertension develops during the use of a COC, the COC must be discontinued and the hypertension treated. If considered appropriate, COC use may be resumed if the blood pressure values return to normal with antihypertensive therapy.
The conditions listed below have been reported to occur or deteriorate both during pregnancy and during administration of COCs. However, there is no conclusive evidence of a correlation between said conditions and the use of COCs: jaundice and/or cholestatic pruritus, gallstone formation, porphyria, systemic lupus erythematosus, haemolytic uraemic syndrome, Sydenham's chorea, herpes gestationis, otosclerosis-related hearing loss.
In women with hereditary angioedema, exogenous oestrogens may induce or aggravate symptoms of angioedema.

Acute or chronic disturbances of liver function may necessitate discontinuation of treatment with COCs until the liver function values return to normal. Recurrence of cholestatic jaundice which manifested first during pregnancy or previous treatment with sex steroids necessitates discontinuation of the COC.

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

During COC use, a worsening of conditions such as endogenous depression, epilepsy, Crohn's disease and ulcerative colitis has been reported.

4.5 Interaction with other medicinal products and other forms of interaction

Note: the prescribing information of concomitant medicinal products must be consulted to identify interactions.

Effects of other medicinal products on Primolut Nor
Interactions can occur with medicinal products that induce microsomal enzymes, which can result in increased clearance of sex hormones and which may lead to changes in the uterine bleeding profile and/or a reduction in the therapeutic effect. Enzyme induction can be observed after just a few days of treatment. Maximum enzyme induction is generally reached within a few weeks. After discontinuation of treatment, enzyme induction may persist for approximately 4 weeks.
Substances increasing the clearance of sex hormones (diminished efficacy of enzyme induction), e.g.:

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

Substances with a variable effect 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 oestrogens and progestogens. 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 or moderate CYP3A4 inhibitors such as azole antifungal agents (e.g. itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of oestrogen or progestogens 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 product containing 0.035 mg ethinylestradiol.

Effects of Primolut Nor on other medicinal products

Progestogens can interfere with the metabolism of other medicinal products. Consequently, plasma and tissue concentrations may either increase (e.g. ciclosporin) 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 the plasma concentration.

Pharmacodynamic Interactions

The concomitant use of 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).
Treatment with Primolut Nor can be resumed 2 weeks after the end of treatment with this combination product.

Other forms of interaction

- **Laboratory tests**

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

4.6 Pregnancy and lactation

The use of Primolut Nor during pregnancy is contraindicated.
Primolut Nor must not be used during lactation (see also section 5.2 "Distribution").

4.7 Effects on ability to drive and use machines

No studies have been conducted on the ability to drive and use machines.

4.8 Undesirable effects

Adverse effects are more common during the first months of administration of Primolut Nor and tend to subside as treatment continues. In addition to the adverse effects listed in section 4.4 "*Special warnings and precautions for use*", the following adverse effects have been reported in women using Primolut Nor, although a causal relationship with the medicinal product cannot always be confirmed.

In the table below, the adverse reactions are listed by MedDRA system organ class (MedDRA SOC). The frequencies are based on data derived from postmarketing experience and from the literature.

System organ class (MedDRA)	**Very Common (≥1/10)**	**Common (≥1/100, <1/10)**	**Uncommon (≥1/1,000, <1/100)**	**Rare (≥1/10,000, <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				Urticaria, rash	

tissue disorders					
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, as well as its synonyms and related conditions.

Other adverse reactions reported are variations in libido, dizziness, nerve irritation phenomena, hirsutism, variations in liver function tests and haemagglutination assays.

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 national reporting system at the following address https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse.

4.9 Overdose
Acute toxicity studies conducted with norethisterone acetate do not indicate risks of acute adverse effects following accidental ingestion of multiple times the 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 potent progestogen. In women pretreated with oestrogens, complete transformation of the endometrium from the proliferative to the secretory state can be achieved with oral administration of 100-150 mg norethisterone per cycle. The progestogenic effects of norethisterone on the endometrium are the basis of the treatment of functional metrorrhagia, primary and secondary amenorrhoea and endometriosis with Primolut Nor.
Inhibition of gonadotropin secretion and suppression of ovulation can be achieved with a daily intake of 0.5 mg norethisterone acetate. The positive effects of Primolut Nor on premenstrual symptoms can be attributed to the suppression of ovarian function.
Due to the stabilising effects of norethisterone on the endometrium, administration of Primolut Nor can be used to regulate the menstrual cycle.
Like progesterone, norethisterone is thermogenic and alters the basal body temperature.

5.2 Pharmacokinetic properties
- **Absorption**

Norethisterone acetate (NETA), administered orally, is absorbed rapidly and completely over a wide dose range. Even during absorption and first passage through the liver, norethisterone acetate is hydrolysed to norethisterone, the active substance of the medicinal product, and acetic acid. Peak serum concentrations of approximately 18 ng/ml (after administration of 5 mg NETA) and 25 ng/ml (after administration of 10 mg NETA) are reached within 2 hours of oral administration

of one Primolut Nor tablet. On the basis of a relative bioavailability study, the drug is released completely from the tablet.

- **Distribution**

Norethisterone binds to serum albumin and to sex hormone-binding globulin (SHBG). Only approximately 3-4% of the total serum drug concentrations are present as free steroid, while approximately 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 serum concentration-time curve of the drug follows a biphasic model. The two phases are characterised by a half-life of 1-3 hours and approximately 5-13 hours.

Norethisterone is secreted in breast milk, where it reaches levels approximately 10% of those found in maternal plasma, regardless of the method of administration. Based on the estimated maximum concentration in maternal serum of approximately 16 ng/ml and daily intake of 600 ml milk by the nursing infant, the latter may receive a maximum of approximately 1 µg norethisterone (0.02% of the maternal dose).

- **Metabolism**

Norethisterone is metabolised mainly 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 form the corresponding sulphates and glucuronides. Some of these metabolites are eliminated rather slowly from plasma, with half-lives of approximately 67 hours. Therefore, during long-term treatment with daily administration of norethisterone, some of these metabolites accumulate in the plasma.

Norethisterone is partially metabolised to ethinylestradiol after oral administration of norethisterone or norethisterone acetate in humans. This transformation results in an ethinylestradiol dose equivalent to 4-6 micrograms per 1 milligram norethisterone / norethisterone acetate administered orally.

- **Elimination**

Norethisterone is not excreted unchanged in significant quantities. The compound is excreted predominantly in the form of A-ring-reduced and hydroxylated metabolites and related conjugates (glucuronides and sulphates) in the urine and faeces in a ratio of approximately 7:3. Most of the renally excreted metabolites are eliminated within 24 hours with a half-life of approximately 19 hours.

- **Steady-state conditions**

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

5.3 Preclinical safety data

Non-clinical data relating to norethisterone or its esters reveal no particular risk to humans based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenic potential that have not already been included in other sections. However, it should be remembered that sex steroids may stimulate the growth of hormone-dependent tissues and tumours.

Reproductive toxicity studies have shown a risk of masculinisation in female foetuses when the medicinal product is administered in high doses during the period of formation of the external genitalia.

Since the epidemiological studies have shown that this effect is also relevant to humans after intake of higher dosages, it must be stated that Primolut Nor can cause signs of virilisation in female foetuses if administered during the hormone-sensitive stage of somatic sexual differentiation (i.e. from Day 45 of pregnancy onwards).

Apart from this, no teratogenic effects have been identified.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate; maize starch; povidone 25; talc; magnesium stearate.

6.2 Incompatibilities
None.

6.3 Shelf life
5 years.

6.4 Special precautions for storage
Protect from light.

6.5 Nature and contents of container
PVC-aluminium blister packs
Pack size: 30 x 10 mg tablets.

6.6 Special precautions for disposal and other handling
No special requirements.

7. MARKETING AUTHORISATION HOLDER
Bayer AG, Kaiser-Wilhelm-Allee 1 - 51373 Leverkusen (Germany)
Local Representative: Bayer S.p.A. - Viale Certosa, 130 - 20156 Milan (MI)

8. MARKETING AUTHORISATION NUMBER
MA no. 021053018

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03.05.1968/01 June 2010

10. DATE OF REVISION OF THE TEXT

05/2020