

PRODUCT INFORMATION

MICRONOR[®] TABLETS norethisterone

Actions

Progestogen-only oral contraceptive containing norethisterone, a synthetic progestogen.

The primary mechanism through which norethisterone prevents conception is not known, but progestogen-only contraceptives are known to alter the cervical mucus, increasing the difficulty of sperm penetration, exert a progestational effect on the endometrium interfering with implantation, and in some patients, suppress ovulation.

Norethisterone is rapidly absorbed from the gastrointestinal tract. Following oral administration, metabolites appear in the urine as conjugated glucuronides and sulphates, with unconjugated metabolites appearing in the faeces.

Pregnancy rates. The pregnancy rate in women using conventional combination oral contraceptives (containing 35 micrograms or more of ethinyloestradiol or 50 micrograms or more of mestranol) is generally reported as less than 1 pregnancy per 100 woman-years of use. Slightly higher rates (somewhat more than 1 pregnancy per 100 woman-years of use) are reported for some combination products containing 35 micrograms or less of ethinyloestradiol, and rates of the order of 3 pregnancies per 100 woman-years of use are reported for the progestogen-only oral contraceptives.

These rates are derived from separate studies conducted by different investigators in several population groups and cannot be compared precisely. Furthermore, pregnancy rates tend to be lower as clinical studies are continued, possibly due to selective retention in the longer studies of those patients who accept the treatment regimen and do not discontinue as a result of adverse reactions, pregnancy or other reasons.

In clinical trials with MICRONOR, 2,963 patients completed 25,901 cycles of therapy and a total of 55 pregnancies were reported. This represents an average pregnancy rate of 2.54 per 100 woman-years. A higher pregnancy rate of 3.72 was recorded in fresh patients (those who had never taken oral contraceptives prior to starting MICRONOR therapy), to a large extent because of incorrect tablet intake. This compares to the lower pregnancy rate of 1.95 recorded in changeover patients (those switched from other oral contraceptives.) This difference was found to be statistically significant. Furthermore, an even greater statistically significant difference in pregnancy rates between two groups found during the first six months of MICRONOR therapy. Therefore it is especially important for fresh patients to strictly adhere to the regimen.

MICRONOR tablet contains the inactive ingredients: lactose anhydrous, magnesium stearate and pregelatinised maize starch.

Indications

Oral contraception.

Contraindications

1. Thrombophlebitis, thromboembolic disorders, cerebral vascular disease, myocardial infarction, or a past history of these conditions.
2. Patients with liver disease or past history of cholestatic jaundice or pruritus of pregnancy and in Dubin-Johnson Syndrome and Rotor Syndrome.

3. Known or suspected carcinoma of the breast and/or genital organs, or known or suspected oestrogen - dependent neoplasia.
4. Undiagnosed abnormal vaginal bleeding.
5. Known or suspected pregnancy.
6. Sickle cell anaemia.
7. Distributed lipid metabolism.
8. History of herpes of pregnancy.
9. Otosclerosis with deterioration in a previous pregnancy.
10. Hypersensitivity to any component of this product.

Warnings

The use of oral contraceptives is associated with increased risks of several serious conditions, including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gall bladder disease, hyperlipidemia and hypertension.

1. Thromboembolic Disorders and Other Vascular Problems

An increased risk of cerebrovascular thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. The increased risk has been estimated to be approximately 4 to 11 times higher for users when compared to non-users.

The risk of thromboembolic and thrombotic disorders, in both users and nonusers of oral contraceptives increases with age. Oral contraceptives are, however, an independent risk factor for these events.

An increased risk of myocardial infarction associated with the use of oral contraceptives has been reported.

The physician and the patient should be alert at the earliest manifestations of thromboembolic and thrombotic disorders (e.g. thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

2. Cigarette Smoking:

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from oral contraceptive use. This risk increases with age particularly after 30 years and with heavy smoking (15 or more cigarettes per day) is quite marked in women over 35 years of age. Women who use oral contraceptives should not smoke.

3. Elevated Blood Pressure

An increase in blood pressure has been reported in patients receiving oral contraceptives. In some women hypertension may occur within a few months of beginning oral contraceptive use. The prevalence in users increases, however, with

longer exposure, and in the fifth year of use is two and a half to three times the reported prevalence in the first year.

4. Ocular Lesions

There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis with the use of oral contraceptives. Discontinue oral contraceptive medication if there is: gradual or sudden, partial or complete loss of vision; proptosis or diplopia; onset or aggravation of migraine or development of headache of a new pattern which is recurrent, persistent or severe; papilloedema; or any evidence of retinal vascular lesions and institute appropriate diagnostic and therapeutic measures.

5. Carcinoma

Several epidemiological studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intra-epithelial neoplasia or invasive cervical cancer. It is not known whether the use of oral contraceptives is causative but an independent association has been consistently shown. The studies suggest that there is an "ever used" effect in addition to duration of use. These findings must be balanced against evidence of significant effects attributable to sexual behaviour, smoking, the presence of human papilloma virus and other factors.

In view of the above, periodical cervical smears should form part of the routine follow up of women who have previously used oral contraceptives. As part of routine patient counselling, advice that hormonal contraceptive does not protect against the transmission of sexually transmissible diseases, including human papilloma virus, should be made clear. (see Precautions)

Close clinical surveillance of all women taking oral contraceptives is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease or abnormal mammograms should be monitored with particular care if they elect to use oral contraceptives instead of other methods of contraception.

6. Hepatic Tumours

Benign hepatic adenomas appear to be associated with the use of oral contraceptives. Although benign, and rare, hepatic adenomas may rupture and may cause death through intra-abdominal haemorrhage. A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives. The relationship of these drugs to this type of malignancy is not known at this time.

7. Birth Defects of Offspring

The use of female sex hormones - both oestrogenic and progestational agents - during early pregnancy may seriously damage the offspring. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with the use of sex hormones, including oral contraceptives, in pregnancy.

8. Gallbladder Disease

Studies report an increased risk of surgically confirmed gallbladder disease in users of oral contraceptives and oestrogens.

9. Carbohydrate and Lipid Effects

A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. For this reason, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives.

10. Bleeding Irregularities

Breakthrough bleeding, spotting, and amenorrhoea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy.

11. Ectopic Pregnancy

Ectopic as well as intrauterine pregnancy may occur in contraceptive failure.

12. Delayed Follicular Atresia/Ovarian Cysts

13. If follicular development occurs, atresia of the follicle is sometimes delayed, and the follicle may continue to grow beyond the size it would attain in a normal cycle. In some cases these enlarged follicles are associated with mild abdominal pain. Rarely they may twist or rupture, requiring surgical intervention.

14. Carcinoma of the Reproductive Organs and Breast

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk of having breast cancer diagnosed in women who are currently using oral contraceptives (OCs).

The most important risk factor for breast cancer in POP users is the age women discontinue the POP; the older the age at stopping, the more breast cancers are diagnosed.

The evidence suggests that compared with never-users, among 10,000 women who use POPs for up to five years but stop by age 20, there would be much less than one extra case of breast cancer diagnosed up to 10 years afterwards. For those stopping by age 30 after 5 years use of the POP, there would be an estimated 2-3 extra cases (additional to the 44 cases of breast cancer per 10,000 women in this age group never exposed to oral contraceptives). For those stopping by age 40 after 5 years use, there would be an estimated 10 extra cases diagnosed up to 10 years afterwards (additional to the 160 cases of breast cancer per 10,000 never-exposed women in this age group).

It is important to inform patients that users of all contraceptive pills appear to have a small increase in the risk of being diagnosed with breast cancer, compared with non-users of oral contraceptives, but this has to be weighed against the known benefits.

15. Headache

The onset or exacerbation of migraine or development of headache with a new pattern, which is recurrent, persistent or severe, requires discontinuation of oral contraceptives and evaluation of the cause.

16. Use in Nursing Mothers

If feasible, the use of oral contraceptives should be deferred until the infant has been weaned. A small fraction of the active ingredients of oral contraceptives have been identified in the milk of mothers receiving these drugs. The effect of these on the infant is unknown. There may be a decrease in the quantity and quality of the milk.

Precautions

1. Before prescribing oral contraceptives, a complete medical and family history and physical examination is desirable, including special reference to blood pressure, breasts, abdomen and pelvic organs, including Papanicolaou smear and laboratory tests. As a general rule oral contraceptives should not be prescribed for longer than one year without another physical examination being performed.
2. The following are some of the medical conditions reported to be influenced by oral contraceptive therapy.
 - a) Under the influence of oestrogen-progestogen preparations pre-existing uterine fibromyomata may increase in size.
 - b) A decrease in glucose tolerance in a significant number of women. (See 'Warnings' 9).
 - c) An increase in blood pressure in a small but significant number of women. (See 'Warnings' 3).
 - d) Cholestatic jaundice. Patients with a history of cholestatic jaundice of pregnancy are more likely to develop cholestatic jaundice during oral contraceptive therapy. If jaundice develops in any patient receiving such drugs, the medication should be discontinued.
 - e) Amenorrhoea during and after oral contraceptive therapy.
 - f) Depression. Patients becoming significantly depressed while taking oral contraceptives should stop the medication and use an alternative method of contraception in order to determine whether the symptom is drug related.
 - g) Other conditions such as epilepsy, migraine, asthma, cardiac or renal dysfunction may be influenced by oral contraceptive therapy. Fluid retention may be a factor.
 - h) An increased risk to sexually transmissible diseases, including human papilloma virus. Patients may not be aware that barrier contraceptive methods are necessary to reduce the risk of transmission of human papilloma virus (See 'Warnings' 5)

3. An increased risk of surgically confirmed gallbladder disease associated with the use of oral contraceptives and oestrogens has been reported (See 'Warnings 8').
4. In breakthrough bleeding, when appearing for the first time in women who have been stabilised and previously well controlled, and in all cases of irregular bleeding per vaginam, organic disease should be excluded.
5. Patients with disease affecting calcium and phosphorous metabolism should be carefully observed whilst on oral contraceptive therapy.
6. Patients should be advised that vulvovaginal candidiasis may occur, in which case they should return for appropriate therapy.
7. Laboratory Data.

Certain endocrine and liver function tests and blood components may be affected by oestrogen-containing oral contraceptives, such as metyrapyrone test: decrease in urinary 17-ketosteroids and 17-ketogenic steroids and pregnanediol determination decrease in urinary pregnanediol levels.

The following laboratory determinations may be altered in patients using oral contraceptives.

Hepatic: Increased BSP retention and other tests, e.g. SGOT & SGPT.

Coagulation: Increased prothrombin, Factors VII, VIII, IX and X; decrease anti-thrombin 3; increased nonadrenaline-induced platelet aggregability.

Endocrine: Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein bound iodine (PBI), T_4 by column, or T_4 by radioimmunoassay, free T_3 resin uptake is decreased, reflecting the elevated TBG, free T_4 concentration is unaltered; decrease in glucose tolerance.

Other: Increase in total phospholipids and triglycerides; decreased serum folate levels; disturbance in normal tryptophan metabolism, which may result in a relative pyridoxine deficiency.

These tests usually return to pre-therapy values after discontinuing oral contraceptive use. However, the physician should be aware that these altered determinations may mask an underlying disease.

Interactions with other medicines

If a woman on norethisterone takes a drug or herbal product that induces an enzyme(s) that metabolizes norethisterone, particularly CYP3A4, she should be counselled to use additional contraception or a different method of contraception. Drugs or herbal products that induce such enzymes may decrease the plasma concentrations of norethisterone, and may decrease the effectiveness of norethisterone or increase breakthrough bleeding. Examples include:

- barbiturates
- bosentan
- carbamazepine
- griseofulvin
- phenytoin

- rifampin
- St. Johns Wort

Some anti-epileptic drugs (AEDs) are known to induce or inhibit a number of hepatic enzymes in the cytochrome P450 system. In drug interaction studies with combined oral contraceptives containing norethisterone, the administration of topiramate (50 mg/day to 800 mg/day) did not significantly affect the exposure of norethisterone.

Significant changes (increase or decrease) in the plasma levels of norethisterone have been noted in some cases of co-administration of HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors (e.g., indinavir and ritonavir).

The therapeutic effect of norethisterone is not affected when activated charcoal is administered 3 hours after the previous dose or 12 hours before the next dose.

An *in vitro* study (Yasuda *et al* 2008) suggests the capacity of nafcillin and dicloxacillin to induce CYP3A4, and both an *in vitro* study (Huwyler *et al* 2006) and *in vivo* study (Cynke *et al* 1999) suggests the capacity of flucloxacillin to induce CYP3A4. There is a possibility that use of such antibiotics concomitantly with norethisterone may increase the clearance of norethisterone and reduce its plasma concentration. This could result in reduced norethisterone contraceptive efficacy. Direct studies exploring this possibility have not been conducted.

Use in Pregnancy

Category D.

MICRONOR is contraindicated during pregnancy.

Many studies have found no effects of foetal development associated with long-term use of contraceptive doses of oral progestogens. The few studies of infant growth and development that have been conducted have not demonstrated significant adverse effects. It is nonetheless prudent to rule out suspected pregnancy before initiating any hormonal contraceptive use.

Use in Lactation

In most women, progestogen-only contraceptives, such as MICRONOR, do not affect the quantity and quality of breast milk or length of lactation. However, isolated post-marketing cases of decreased milk production have been reported. Studies with various orally administered progestogen-only contraceptives have shown that small amounts of progestogens pass into the breast milk of nursing mothers resulting in detectable steroid levels in infant plasma. No adverse effects have been found on the health, growth or development of the infant.

Adverse Reactions

Postmarketing Experience:

Adverse drug reactions first identified during post-marketing experience with norethisterone are included in Table 1; the frequencies are provided according to the following convention:

Very common $\geq 1/10$

Common $\geq 1/100$ and $< 1/10$

Uncommon $\geq 1/1,000$ and $< 1/100$

Rare $\geq 1/10,000$, $< 1/1,000$

Very rare $< 1/10,000$, including isolated reports

Unknown (cannot be estimated from the available data)

Table 1. Adverse Drug Reactions Identified During Post-Marketing Experience with MICRONOR[®] by Frequency Category Estimated from Spontaneous Reporting Rates

<u>Immune System Disorders</u>	
<u>Very rare</u>	<u>Anaphylactic/Anaphylactoid reaction, Hypersensitivity</u>
<u>Gastrointestinal Disorders</u>	
<u>Very rare</u>	<u>Abdominal pain</u>
<u>Hepatobiliary Disorders</u>	
<u>Very rare</u>	<u>Hepatitis, Jaundice cholestatic</u>
<u>Skin and Subcutaneous Tissue Disorders</u>	
<u>Very rare</u>	<u>Alopecia, Rash, Rash pruritic</u>
<u>Pregnancy, Puerperium and Perinatal Conditions</u>	
<u>Very rare</u>	<u>Ectopic pregnancy</u>
<u>Reproductive System and Breast Disorders</u>	
<u>Very rare</u>	<u>Breast pain, Menstruation delayed, Menstruation irregular, Ovarian cyst, Suppressed lactation, Vaginal haemorrhage, Menorrhagia, Withdrawal bleed when product is stopped</u>

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (See 'Warnings'): thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral haemorrhage, hypertension, gall bladder disease, congenital anomalies.

There is evidence of an association between oral contraceptive use and mesenteric thrombosis, benign hepatomas and neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug related: nausea, vomiting reaction, occurring in approximately 10% or less of patients during the first cycle.

Less common reactions include: gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, amenorrhoea during and after treatment, temporary infertility after discontinuance of treatment, oedema, chloasma or melasma which may persist, breast changes: tenderness, enlargement and secretion, change in weight (increase or decrease), change in cervical erosion and cervical secretion, possible diminution in lactation when given immediately post partum, cholestatic jaundice, migraine, increase in size of uterine fibromyomata, rash (allergic), mental depression, reduced tolerance to carbohydrates, vaginal candidiasis. Decreased lactation has been reported very rarely.

The following adverse reactions have also been reported in users of oral contraceptives: premenstrual-like syndrome, intolerance to contact lenses, change in corneal curvature (steepening), cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, acne, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, haemorrhagic eruption, vaginitis, porphyria, impaired renal function.

Dosage and Administration

To achieve maximum contraceptive effectiveness, MICRONOR tablets must be taken exactly as directed. Tablets should be taken at the same time every day and continued daily. MICRONOR is administered on a continuous daily dosage regimen starting on the first day of

menstruation, i.e. 1 tablet each day, every day of the year. The patient should be advised that if prolonged bleeding occurs she should consult her physician.

The use of MICRONOR for contraception maybe initiated postpartum (see Warnings). When MICRONOR is administered during the post partum period, the increase risk of thromboembolic disease associated with the postpartum period must be considered. (See Contraindications, Warnings, and Precautions concerning thrombembolic disease.)

In the case of missed tablets

If one tablet has been missed, or there is a delay of more than 3 hours but less than 24 hours in taking the tablet, the missed tablet should be taken as soon as the delay is recognised (catch-up dose) and the next scheduled tablet should be taken at the usual time, even if that means taking two tablets in the one day. Based on the duration of cervical mucus changes following progestogen-only oral contraceptive tablet ingestion, whenever a tablet is taken 3 or more hours late, a reliable supplementary non-hormonal contraceptive method should be used in addition to MICRONOR, for the next 48 hours following the catch-up dose. If a patient misses one complete day, she should take two tablets as soon as possible, and then resume taking the pills according to her regular dosing schedule. She should also consult her physician.

If there is a delay in taking the tablet of more than 24 hours, pregnancy is possible. MICRONOR is contraindicated in pregnancy. MICRONOR should be ceased and a reliable non-hormonal method of contraception should be used until menses appear or pregnancy has been accurately excluded.

Alternatively, if the patient has taken the tablets correctly and if menses do not appear when expected, a non-hormonal method of contraception should be substituted until an appropriate diagnostic procedure is performed to rule out pregnancy.

Breakthrough bleeding or spotting

In the event of breakthrough bleeding or spotting, treatment should be continued. Breakthrough bleeding is common among women using progestogen-only oral contraceptives. If breakthrough bleeding persists, or is accompanied by abdominal pain, additional medical evaluation should be considered. In undiagnosed persistent or recurrent abnormal bleeding from the vagina adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another formulation may solve the problem.

In the case of vomiting and diarrhoea

Vomiting and diarrhoea may reduce the effectiveness of oral contraceptive pills and increase the possibility of pregnancy. In cases where vomiting or diarrhoea has occurred within 2 hours of tablet intake, the woman should attempt to take an extra pill as soon as she is able. Continue taking the tablets on schedule if possible.

If the woman is unable to take an extra MICRONOR pill within 2 hours of her regularly scheduled dose, MICRONOR should be ceased and she should use a reliable non-hormonal method of contraception until menses appear or pregnancy has been accurately excluded.

As with all oral contraceptives, women who use MICRONOR should be advised that it does not protect against HIV infection (AIDS) and other sexually transmissible diseases (STDs). Additional measures are required to prevent the transmission of STDs.

Use of MICRONOR in the event of a missed menstrual period

1. If the patient has not adhered to the prescribed dosage regimen, the possibility of pregnancy should be considered after 45 days from the last menstrual period. MICRONOR should be withheld until pregnancy has been ruled out.

2. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen.

Overdosage

Although, no serious ill effects have been reported following acute ingestion of large doses of oral contraceptives, there are no data specific to MICRONOR overdosage. Overdosage may cause nausea, vomiting and, in young girls, vaginal bleeding. There are no antidotes and treatment should be symptomatic.

Presentation

Tablets, 350 micrograms (white, marked C035 each side): 4 x 28's.

Sponsor

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