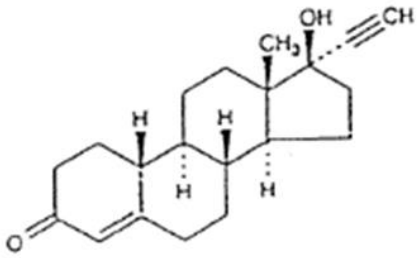
PRODUCT INFORMATION

BREVINOR® 28 DAY TABLETS

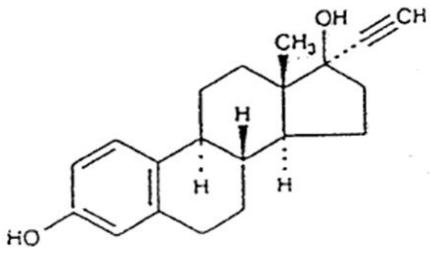
BREVINOR-1® 28 DAY TABLETS

NAME OF THE MEDICINE

Norethisterone and Ethinyloestradiol



Norethisterone
CAS: 68-22-4



Ethinyloestradiol
CAS: 57-63-6

DESCRIPTION

Norethisterone is a progestogen. It is a white to creamy-white odourless crystalline powder with a slightly bitter taste, insoluble in water and sensitive to light.

Ethinyloestradiol is an oestrogen. It is a fine, white odourless, crystalline powder almost insoluble in water and sensitive to light.

Each BREVINOR 28 DAY package contains 21 blue active tablets and 7 orange placebo tablets.

Each BREVINOR-1 28 DAY package contains 21 white active tablets and 7 orange placebo tablets.

Each blue active tablet contains norethisterone 500 μg and ethinyloestradiol 35 μg and the excipients: magnesium stearate, povidone, maize starch, lactose and indigo carmine.

Each white active tablet contains norethisterone 1 mg and ethinyloestradiol 35 μg and the excipients: magnesium stearate, povidone, maize starch and lactose.

Each orange placebo tablet contains magnesium stearate, lactose, microcrystalline cellulose and sunset yellow FCF.

PHARMACOLOGY

Pharmacological Class: synthetic steroidal combination oral contraceptives (COC).

Oestrogenic, progestational and antigonadotrophic characteristics are revealed by the endocrine profile of these combinations.

Like other combination type pills (oestrogen and progestogen combination), BREVINOR and BREVINOR-1 produce a contraceptive effect primarily by suppressing the hypothalamic-pituitary system resulting in prevention of ovulation. The oestrogenic compound, ethinyloestradiol acts by suppressing secretion of follicle stimulating hormone (FSH), resulting in prevention of follicle development and the rise of plasma oestradiol which is thought to be the stimulus for releasing luteinising hormone (LH). The progestogenic compound, norethisterone, primarily acts by inhibiting the pre-ovulatory rise of LH. Long-term administration of combination type oral contraceptives may also produce a direct effect on ovarian steroidogenesis or the response of the ovary to gonadotrophins. Although the primary mechanism of action is inhibition of ovulation, alterations in the genital tract including changes in the cervical mucus (which increase the difficulty of sperm penetration) and the endometrium (which reduce the likelihood of implantation) may also contribute to contraceptive effectiveness. Studies using ^{14}C labelled compounds have shown that both norethisterone and ethinyloestradiol are rapidly absorbed from the gastrointestinal tract. Following oral administration, metabolites of both compounds appear in the urine as conjugated glucuronides and sulfates, with unconjugated metabolites appearing in the faeces.

CLINICAL TRIALS

Different pregnancy and adverse reaction rates have been reported with the use of each oral contraceptive. In as much as these rates are usually derived from separate studies conducted by different investigators in several population groups, they cannot be compared with precision. Furthermore, pregnancy and adverse reaction rates tend to be lower as clinical experience is expanded, possibly due to retention in the clinical study of those patients who accept the treatment regimen and did not discontinue due to adverse reactions or pregnancy.

In clinical trials with BREVINOR tablets, 1,168 patients completed 16,345 cycles of use, and a total of three pregnancies were reported. In each case, the tablets were not taken as directed. This represents a pregnancy rate of 0.22 per 100 women years. In clinical trials with BREVINOR-1 tablets, 940 patients completed 14,366 cycles of use and a total of two pregnancies were reported. In each case, the tablets were not taken as directed. This represents a pregnancy rate of 0.17 per 100 women years.

INDICATIONS

Contraception.

CONTRAINDICATIONS

BREVINOR or BREVINOR-1 should not be used in the presence of any of the conditions listed below. Should any of the conditions appear for the first time during BREVINOR or BREVINOR-1 use, the product should be stopped immediately.

- Presence or risk of venous thromboembolism (VTE) (see **PRECAUTIONS**);
  - Current VTE (on anticoagulants) or history of deep venous thrombosis (DVT) or pulmonary embolism (PE) or other thrombotic disorder;
  - Known hereditary or acquired predisposition for venous thromboembolism, such as APC-resistance (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency;
  - Major surgery with prolonged immobilisation;
  - A high risk of venous thromboembolism due to the presence of multiple risk factors.
- Presence or risk of arterial thromboembolism (ATE) (see **PRECAUTIONS**);
  - Current ATE or history of ATE (e.g. myocardial infarction or stroke) or prodromal condition (e.g. angina pectoris or transient ischaemic attack ([TIA]);
  - Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (eg. anticardiolipin-antibodies and lupus anticoagulant);
  - History of migraine with focal neurological symptoms;
  - A high risk of arterial thromboembolism due to multiple risk factors or to the presence of one serious risk factor such as:
    - Diabetes mellitus with vascular symptoms;
    - Severe hypertension;
    - Severe dyslipoproteinaemia;
    - Sickle cell anaemia.
- Pancreatitis or a history thereof if associated with severe hypertriglyceridemia;
- Presence or history of severe hepatic disease so long as liver function has not returned to normal, history of cholestatic jaundice or pruritis in pregnancy, jaundice with oral contraceptive use, Dubin -Johnson Syndrome, Rotor Syndrome;
- Presence or history of liver tumours (benign or malignant);
- Known or suspected sex steroid-influenced malignancies (e.g. of the genital organs or the breasts);
- Undiagnosed vaginal bleeding;
- Known or suspected pregnancy;
- History of herpes in pregnancy, history of otosclerosis with exacerbations in pregnancy;
- Hypersensitivity to any of the ingredients contained in BREVINOR or BREVINOR-1.

PRECAUTIONS

If any of the conditions/risk factors mentioned below are present, the benefits of BREVINOR or BREVINOR-1 should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start taking it. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her doctor. The doctor should then decide whether BREVINOR or BREVINOR-1 should be discontinued.

Circulatory Disorders

Risk of venous thromboembolism (VTE)

The use of any COC increases the risk of VTE compared with no use. The women considering using BREVINOR or BREVINOR-1should be advised that her VTE risk is highest in the first ever year of use and that there is some evidence that the risk is increased when a COC is re-started after a break in use of 4 weeks or more.

It is important that women understand that VTE associated with COC use is rare in average-risk women. The risk in pregnancy (5 - 20 per 10,000 women over 9 months) and the risk in the post-partum period (45 - 65 per 10,000 women over 12 weeks) is higher than that associated with COC use. The risk of VTE with the COC is greatest for products containing over 50 µg of ethinlyoestradiol. There is less risk for products such as BREVINOR or BREVINOR-1 containing less than 35 µg ethinyloestradiol. Products that contain the progestagen norethisterone are associated with the lowest risk of VTE. The lowest dose of norethisterone tolerated should be prescribed.

The decision to use any product other than one with the lowest VTE risk should be taken only after a discussion with the woman to ensure she understands the risk of VTE with COCs, and how her current risk factors influence this risk.

Risk[1] of developing a blood clot (VTE) in a year

Women not using a combined hormonal contraceptive and not pregnant	About 2 out of 10,000 women[1]
Women using a COC containing levonorgestrel, norethisterone or norgestimate	About 5 - 7 out of 10,000 women
Women using a COC containing etonogestrel or norelgestromin	About 6 - 12 out of 10,000 women
Women using a COC containing drospirenone, gestodene, desogestrel or cyproterone[2]	About 9 - 12 out of 10,000 women
Women using a COC containing chlormadinone, dienogest or nomegestrol	Not yet known[3]

[1] In any individual woman the risk may be far higher, depending on her underlying risk factors (see below).

[2] While cyproterone is indicated for the treatment of moderate to severe acne related to androgen sensitity and/or hirsutism, it is known to have efficacy as a contraceptive. The risk of VTE associated with cyproterone use is considered to be 1.5 to 2 times higher than for COCs containing levonorgestrel and may be similar to the risk with contraceptives containing gestodene, desogestrel or drospirenone.

[3] Further studies are ongoing or planned to collect sufficient data to estimate the risk for these products. Where the risk for a particular progestogen is uncertain, the risk of the class should be used in determining the risk for the individual patient.

The increased risk of VTE during the postpartum period must be considered if restarting BREVINOR or BREVINOR-1 at this time.

VTE is a serious condition and may be fatal in 1-2% of cases. Extremely rarely, thrombosis has been reported to occur in COC users in other blood vessels, e.g. hepatic, mesenteric, renal or retinal veins and arteries.

The risk for venous thromboembolic complications in COC users may increase substantially in a woman with additional risk factors, particularly if there are multiple risk factors (see list below).

BREVINOR or BREVINOR-1 is contraindicated if a woman has multiple risk factors that put her at high risk of venous thrombosis. If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors – in this case her total risk of VTE should be considered. If the balance of benefits and risks is considered to be negative a COC should not be prescribed.

Risk factors for VTE

- Obesity (body mass index over 30 kg/m²). Risk increases substantially as BMI rises;
- Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma;
- Temporary immobilisation including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors;
- Positive family history (venous thromboembolism ever in a sibling or parent especially at a relatively early age e.g. before 50);
- Biochemical factors Activated Protein C (APC) resistance (including Factor V Leiden), antithrombin-III deficiency, protein C deficiency, protein S deficiency;
- Other medical conditions associated with VTE:
  - Cancer;
  - Systemic lupus erythematosus;
  - Haemolytic uraemic syndrome;
  - Chronic inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis);
  - Sickle cell disease.
- Increasing age, particularly above 35 years;
- Smoking.

In women at risk of prolonged immobilisation (including major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma), it is advisable to discontinue use of BREVINOR or BREVINOR-1 (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation. Another method of contraception should be used to avoid unintentional pregnancy. Antithrombotic treatment should be considered if BREVINOR or BREVINOR-1 has not been discontinued in advance.

If a hereditary predisposition to VTE is suspected, the woman should be referred to a specialist for advice before deciding about any COC use.

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

Symptoms of VTE (deep vein thrombosis and pulmonary embolism)

Women should be informed of the symptoms of VTE and be advised to seek urgent medical attention if VTE symptoms develop and to inform the healthcare professional that she is taking a COC.

Symptoms of deep vein thrombosis (DVT) can include:

- Unilateral swelling of the leg and/or foot 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 discoloured 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 be associated with haemoptysis;
- Sharp chest pain;
- 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).

Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discoloration of an extremity.

If the occlusion occurs in the eye symptoms can range from painless blurring of vision which can progress to loss of vision. Sometimes loss of vision can occur almost immediately.

Risk of arterial thromboembolism (ATE)

Epidemiological studies have associated the use of COCs with an increased risk for arterial thromboembolism (e.g. myocardial infarction, angina pectoris, stroke or TIA). Arterial thromboembolic events may be fatal.

The risk of arterial thromboembolic complications in COC users increases in women with risk factors. BREVINOR or BREVINOR-1 is contraindicated if a woman has one serious or multiple risk factors for ATE that puts her at high risk of arterial thrombosis. If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors - in this case her total risk should be considered. If the balance of benefits and risks is considered to be negative a COC should not be prescribed.

Risk factors for ATE

- Increasing age, particularly above 35 years;

- Smoking;
- Hypertension;
- Obesity;
- Positive family history (arterial thromboembolism ever in a sibling or parent especially at relatively early age e.g. below 50);
- Biochemical factors: hyperhomocysteinaemia and antiphospholipid antibodies (e.g. anticardiolipin antibodies~~,~~ and lupus anticoagulant);
- Migraine;
- Other medical conditions associated with adverse vascular events:
  - Diabetes mellitus;
  - Hyperhomocysteinaemia;
  - Valvular heart disease;
  - Atrial fibrillation;
  - Dyslipoproteinaemia;
  - Systemic lupus erythematosus.

Women should be advised not to smoke if they wish to use a COC. Women over 35 years of age who continue to smoke should be strongly advised to use a different method of contraception.

If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any COC use.

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.

Symptoms of ATE

Women should be informed of the symptoms of ATE and be advised to seek urgent medical attention if ATE symptoms develop and to inform the healthcare professional that she is taking a COC.

Symptoms of a stroke can include:

- Sudden numbness or weakness of the face, arm or leg, especially on one side of the body;
- Sudden trouble walking, dizziness, loss of balance or coordination;
- Sudden confusion, trouble speaking or understanding;
- Sudden trouble seeing in one or both eyes;
- Sudden, severe or prolonged headache with no known cause;
- Loss of consciousness or fainting with or without seizure.

Temporary symptoms suggest the event is a transient ischaemic attack (TIA).

Symptoms of myocardial infarction (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;
- Feeling of being full, having indigestion or choking;
- Sweating, nausea, vomiting or dizziness;
- Extreme weakness, anxiety, or shortness of breath;
- Rapid or irregular heartbeats.

Persistence of Risk of Vascular Disease

There are three studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women 40-49 years who had used oral contraceptives for 5 or more years, but this increased risk was not demonstrated in other age groups. In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small. Subarachnoid haemorrhage also has a significantly increased relative risk after termination of use of oral contraceptives. However, these studies were performed with oral contraceptive formulations containing 0.05 mg or higher of oestrogen.

Estimates of Mortality from Contraceptive Use

One study gathered data from a variety of sources which have estimated the mortality rates associated with different methods of contraception at different ages. These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth. The observation of a possible increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970's but not reported in the U.S. until 1983. However, current clinical practice involves the use of lower oestrogen dose formulations combined with careful restriction of oral contraceptive use to women who do not have the various risk factors listed in this document.

Because of these changes in practice and, also, because of some limited new data which suggest that the risk of cardiovascular disease with the use of oral contraceptives may now be less than previously observed, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the topic in 1989. The committee concluded that although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy non smoking women (even with the newer low-dose formulations), there are greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means of contraception.

Therefore, the Committee recommended that the benefits of oral contraceptive use by healthy non-smoking women over 40 may outweigh the possible risks. Of course, older women, as all women who take oral contraceptives, should take the lowest possible dose formulation that is effective.

Carcinoma of the Breast and Reproductive Organs

Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian and cervical cancer in women using oral contraceptives.

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 the 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 the routine counselling, advice that hormonal contraception does not protect against the transmission of sexually transmittable diseases, including human papilloma virus, should be made clear. Patients may not be aware that barrier contraceptive measures are necessary to reduce the risk of transmission of human papilloma virus.

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 combined oral contraceptives. The excess risk gradually disappears during the course of the ten years after cessation of combined oral contraceptive use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent combined oral contraceptives 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 combined oral contraceptives users, the biological effects of combined oral contraceptives 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.

In spite of many studies of the relationship between oral contraceptive use and breast or cervical cancers, a cause and effect relationship has not been established.

Hepatic Neoplasia

Benign hepatic adenomas are associated with oral contraceptive use although the incidence of benign tumours is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases per 100,000 for users, a risk that increases after 4 or more years of use. Rupture of rare, benign, hepatic adenomas may cause death through intra abdominal haemorrhage.

Studies in the United States and Britain have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) oral contraceptive users. However, these cancers are extremely rare in the United States and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users is less than 1 per 1,000,000 users.

Ocular Lesions

There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision;

onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

Gallbladder Disease

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and oestrogen. More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal. The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of oestrogen and progestogens.

Carbohydrate and Lipid Metabolic Effects

Oral contraceptives have been shown to impair oral glucose tolerance. Oral contraceptives containing greater than 0.075 mg of oestrogen cause glucose intolerance with impaired insulin secretion, while lower doses of oestrogen may produce less glucose intolerance. Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents. However, in the non-diabetic woman, oral contraceptives appear to have no effect on fasting blood glucose. Because of these demonstrated effects, prediabetic and diabetic women should be carefully observed while taking oral contraceptives. Some women may develop persistent hypertriglyceridemia while on the pill. As discussed earlier (see **CONTRAINDICATIONS**), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.

Elevated Blood Pressure

An increase in blood pressure has been reported in women taking oral contraceptives. The incidence of risk also was reported to increase with continued use and among older women. Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing concentrations of progestogens.

Women with a history of hypertension or hypertension-related diseases or renal disease should be encouraged to use another method of contraception. If women elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives and there is no difference in the occurrence of hypertension among ever- and never-users.

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.

Bleeding Irregularities

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first 3 months of use. Non-hormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea pregnancy should be ruled out.

Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was pre-existent.

Sexually Transmitted Diseases

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Vomiting and/or Diarrhoea

Diarrhoea and/or vomiting may reduce hormone absorption resulting in decreased serum concentrations (see **DOSAGE AND ADMINISTRATION**).

General

i. PHYSICAL EXAMINATION AND FOLLOW-UP

It is good medical practice for all women to have annual history and physical examinations, including women using oral contraceptives. The physical examination, however, may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the clinician. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

ii. LIPID DISORDERS

Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult.

iii. LIVER FUNCTION

If jaundice develops in any woman receiving oral contraceptives the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function.

iv. FLUID RETENTION

Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

v. EMOTIONAL DISORDERS

Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

vi. CONTACT LENSES

Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

vii. Pre-existing uterine fibromyomata may increase in size.

viii. Other conditions such as epilepsy, migraine, asthma, cardiac or renal dysfunction may be influenced by oral contraceptive therapy.

ix. Because oestrogens may hasten epiphyseal closure, oral contraceptives should be used judiciously in young patients in whom bone growth is not complete.

x. Patients should be advised that vulvovaginal candidiasis may occur, in which case they should return for appropriate therapy.

Ectopic Pregnancy

Ectopic as well as intra-uterine pregnancy may occur in contraceptive failures. However, in oral contraceptive failures, the ratio of ectopic to intra-uterine pregnancies is higher than in women who are not receiving oral contraceptives, since the drugs are more effective in preventing intra-uterine than ectopic pregnancies. The higher ectopic/intra-uterine ratio has been reported with both combination products and progestogen-only oral contraceptives.

Use in Pregnancy

PREGNANCY CATEGORISATION: B3

Animal studies have shown that high doses of progestogens can cause masculinization of the female fetus. The results from these experiments in animals do not seem to be relevant to humans, because of the low doses used in contraceptives. There is no conclusive evidence that intake of oral contraceptives during pregnancy represents an increased risk to the fetus.

Use in Lactation

Small amounts of oral contraceptive steroids have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use oral contraceptives but to use other forms of contraception until she has completely weaned her child.

Effects on Laboratory Tests

Certain endocrine and liver function tests and blood components may be affected by oral contraceptives:

- Increased prothrombin and factors VII, VIII, IX, and X;
- Decreased antithrombin 3;
- Increased noradrenaline-induced platelet aggregability;

- Increased thyroid binding globulin (TGB) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 concentration is unaltered;

- Other binding proteins may be elevated in serum;

- Sex steroid binding globulins are increased and result in elevated levels of total circulating sex steroids and corticoids; however, free or biologically active levels remain unchanged;

- Triglycerides may be increased;

- Glucose tolerance may be decreased; and

- Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

INTERACTIONS WITH OTHER MEDICINES

Reduced efficacy and increased incidence of breakthrough bleeding and menstrual irregularities have been associated with concomitant use of rifampicin. A similar association though less marked, has been suggested with barbiturates, phenylbutazone, phenytoin sodium, and possibly with griseofulvin, ampicillin, tetracyclines, carbamazepine, oxacillin and trimethoprim sulfamethoxazole. Oral contraceptives may be also affected by the enzyme induction of St John's wort (*hypericum perforatum*). This may reduce the contraceptive efficacy.

ADVERSE REACTIONS

The following adverse events have been reported in patients receiving oral contraceptives:

Vascular disorders: arterial thromboembolism, cerebral haemorrhage, cerebral thrombosis, mesenteric thrombosis, pulmonary embolism, retinal thrombosis, thrombophlebitis.

Reproductive disorders: amenorrhoea, breakthrough bleeding, breast enlargement, breast secretion, breast tenderness, change in cervical erosion and secretion, change in menstrual flow, diminution in lactation when given immediately postpartum, spotting, temporary infertility after discontinuation of treatment, change in libido, pre-menstrual syndrome.

Gastrointestinal disorders: gastrointestinal symptoms such as abdominal cramps and bloating, nausea, vomiting, colitis, dyspepsia, inflammatory bowel disease (Crohn's disease, ulcerative colitis).

Skin disorders: melasma which may persist, rash (allergic), acne, chloasma, erythema multiforme, erythema nodosum, haemorrhagic eruption, photosensitivity.

Vision disorders: change in corneal curvature (steepening), intolerance to contact lenses, cataracts.

Myo, endo, pericardial, and valve disorders: myocardial infarction, hypertension.

Neoplasm: hepatic adenomas, carcinomas, or benign liver tumours.

Body as a whole: decrease or increase in weight, oedema, hirsutism, loss of scalp hair, leg cramps, Vitamin B6 deficiency, backache.

Liver and biliary disorders: gallbladder disease, cholestatic jaundice, Budd-Chiari syndrome, porphyria.

Nervous system disorders: migraine, headache, nervousness, dizziness, fatigue.

Psychiatric disorders: mental depression.

Metabolic disorders: reduced tolerance to carbohydrates, changes in appetite.

Resistance mechanism disorders: vaginal candidiasis, vaginitis.

Urinary system disorders: impaired renal function, cystitis-like syndrome, hemolytic uraemic syndrome.

The most serious adverse reactions associated with the use of oral contraceptives are indicated under **PRECAUTIONS** and **CONTRAINDICATIONS**).

DOSAGE AND ADMINISTRATION

BREVINOR 28 Day Pack

To achieve maximum contraceptive effectiveness, BREVINOR 28 day must be taken as directed and at daily intervals not exceeding 24 hours. Women should be instructed to take the tablets at the same time every day, preferably at bedtime.

First Cycle: On the first day of the menstrual cycle, i.e. the first day of bleeding, the woman is instructed to take a blue active tablet corresponding to the day of the week from the green area of the BREVINOR 28 day pack. Thereafter one blue active tablet is taken daily, following the arrows on the pack, until all 21 blue tablets have been taken. The woman should then be instructed to take one orange inactive tablet daily for the next seven days. Withdrawal bleeding should usually occur within two to four days after the last blue active tablet has been taken. The woman should be advised that her first cycle after taking all BREVINOR 28 day tablets is likely to be shorter than usual, i.e. approximately 23 to 24 days. Thereafter, her cycles should return to normal, approximately 28 days.

The next and all subsequent courses of BREVINOR 28 day will begin on the day after the last pack was completed, even if withdrawal bleeding is still in progress. Each course of BREVINOR 28 day is begun on the same day of the week as the first course, always beginning with a blue active tablet from the green area.

BREVINOR 28 day is effective from the first day if taken as described above.

Changing From Another Pill: If a woman is switching to BREVINOR 28 day from another 28 day oral contraceptive pack, then all tablets in the current 28 day pack should be finished and BREVINOR 28 day started on the next day by taking a blue active tablet which corresponds to the day of the week, from the green area of the pack. During the first BREVINOR 28 day cycle, a non-hormonal contraceptive method (other than the rhythm or temperature method), should be used until seven consecutive blue active tablets have been taken. During this changeover, a period of shortened duration or no period may occur.

If a woman is switching to BREVINOR 28 day from a 21 day oral contraceptive pack, then the woman should wait seven days from when the last active tablet was taken from the old pack and start the new BREVINOR 28 day pack on the eighth day by taking a blue active tablet which corresponds to the day of the week, from the green area of the pack. A non-hormonal contraceptive method (other than the rhythm or temperature method) should be used during the first BREVINOR 28 day cycle, until seven consecutive blue active tablets have been taken.

BREVINOR-1 28 Day Pack

To achieve maximum contraceptive effectiveness, BREVINOR-1 28 day must be taken as directed and at daily intervals not exceeding 24 hours. Women should be instructed to take the tablets at the same time every day, preferably at bedtime.

First Cycle: On the first day of the menstrual cycle, i.e. the first day of bleeding, the woman is instructed to take a white active tablet corresponding to the day of the week from the green area of the BREVINOR-1 28 day pack. Thereafter one white active tablet is taken daily, following the arrows on the pack, until all 21 white tablets have been taken. The woman should then be instructed to take one orange inactive tablet daily for the next seven days. Withdrawal bleeding should usually occur within two to four days after the last white tablet has been taken. The woman should be advised that her first cycle after taking all BREVINOR-1 28 day tablets is likely to be shorter than usual, i.e. approximately 23 to 24 days. Thereafter, her cycles should return to normal, approximately 28 days.

The next and all subsequent courses of BREVINOR-1 28 day will begin on the day after the last package was completed, even if withdrawal bleeding is still in progress. Each course of BREVINOR-1 28 day is begun on the same day of the week as the first course, always beginning with a white active tablet from the green area.

BREVINOR-1 28 day is effective from the first day if taken as described above.

Changing From Another Pill: If a woman is switching to BREVINOR-1 28 day from another 28 day oral contraceptive pack, then all tablets in the current 28 day pack should be finished and BREVINOR-1 28 day started on the next day by taking a white active tablet which corresponds to the day of the week, from the green area of the pack. During the first BREVINOR-1 28 day cycle, a non-hormonal contraceptive method (other than the rhythm or temperature method), should be used until seven consecutive white active tablets have been taken. During this changeover, a period of shortened duration or no period may occur.

If a woman is switching to BREVINOR-1 28 day from a 21 day oral contraceptive pack, then the woman should wait seven days from when the last active tablet was taken from the old pack and start the new BREVINOR-1 28 day pack on the eighth day by taking a white active tablet which corresponds to the day of the week, from the green area of the pack. A non-hormonal contraceptive method (other than the rhythm or temperature method) should be used during the first BREVINOR-1 28 day cycle, until seven consecutive white active tablets have been taken.

If transient spotting or breakthrough bleeding occurs with either BREVINOR 28 day or BREVINOR-1 28 day, the woman is instructed to continue the regimen since such bleeding is usually without significance. If the bleeding is persistent or prolonged, the woman is advised to consult her physician.

BREVINOR 28 day or BREVINOR-1 28 day can be prescribed postpartum for the nonlactating mother or postabortum as soon as the first normal menstrual period following a normal biphasic cycle occurs. If a further pregnancy is contraindicated for medical reasons, medication with BREVINOR 28 day or

BREVINOR-1 28 day must be initiated by the 12th (but not before the 7th) day postpartum, or immediately postabortum or by the 5th day postabortum at the latest. When oral contraceptives are administered in the immediate postpartum/postabortum period, the increased risk of thromboembolic disease must be considered.

Missed Tablets: If the woman is less than 12 hours late in taking one of her blue or white active tablets, she should take this tablet at once and then take the next one at her usual time. If the woman is more than 12 hours late in taking one of her blue or white active tablets, she should continue to take her tablets daily as usual, ignoring the missed tablet or tablets, but also take extra contraceptive precautions (other than the rhythm or temperature method) for the next seven days. If these seven days extend into the inactive orange tablet section she should start a new pack on the next day after having taken the last blue or white active tablet from the green section of the current pack (i.e. skip the orange inactive tablets). This will mean that the woman may not have a period until the end of two packs. However, if the woman misses one or more orange inactive tablets, she will be protected against pregnancy provided she begins the active tablets on the appropriate day.

If the woman has not adhered to the prescribed regimen (missed one or more active tablets or started taking them on a day later than recommended), the probability of pregnancy should be considered at the time of the first missed period before BREVINOR 28 day or BREVINOR-1 28 day is resumed. In the case of the continuous intake of active tablets from two packs of BREVINOR 28 day or BREVINOR-1 28 day (see before), a period should occur at the end of the second pack. If it does not, pregnancy should be ruled out before BREVINOR 28 day or BREVINOR-1 28 day is resumed.

Concurrent Medication: If the woman is taking other drugs that may interact with norethisterone or ethinyloestradiol from her 28 day pack, then she should continue to take her tablets as usual but also employ a nonhormonal method of contraception (other than the rhythm or temperature method) during the time she is taking the interacting medication and continue for seven days after the medication is stopped. If these seven days extend into the inactive orange tablet section, the woman should start a new pack on the next day after having taken the last blue or white active tablet from the green section of the current pack (i.e. skip the orange inactive tablets). This will mean that the woman may not have a period until the end of two packs. If the woman is taking interacting medications on a chronic basis, another method of contraception should be considered.

Vomiting or Diarrhoea: Mild laxatives do not impair the effectiveness of BREVINOR 28 day or BREVINOR-1 28 day. If, however, vomiting or diarrhoea occur during or shortly after the intake of BREVINOR 28 day or BREVINOR-1 28 day contraceptive reliability may be jeopardised. Tablet taking should not be interrupted, to avoid premature withdrawal bleeding. A non-hormonal method of contraception (other than the rhythm or temperature method) should be employed during the period of vomiting or diarrhoea and continued for seven days following the gastrointestinal upset. If these seven days extend into the inactive orange tablet section, the woman should start a new pack on the next day after having taken the last active tablet from the green sectionof the current pack (i.e. skip the orange inactive tablets). This will mean that the woman may not have a period until the end of two packs. If the circumstance reducing the effectiveness of BREVINOR 28 day or BREVINOR-1 28 day is protracted, other methods of contraception should be considered.

OVERDOSAGE

Exact toxic doses have not been determined. When oral contraceptives are the sole medication taken as an acute overdose, the patient may remain clinically well. Overdosage may cause nausea, vomiting, breast distension, and withdrawal bleeding may occur in females.

In the case of overdosage or accidental ingestion, the patient should be observed and given supportive treatment, as there is no specific antidote. Contact the Poisons Information Centre on 13 11 26 for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

BREVINOR and BREVINOR-1 tablets are presented in PVC/aluminium blister.

BREVINOR 28 DAY Each blister contains 21 blue active tablets and 7 orange placebo tablets.

BREVINOR-1 28 DAY Each blister contains 21 white active tablets and 7 orange placebo tablets.

One# and four month packs contain 1 and 4 blisters respectively.

not currently available.

Storage Conditions

Stored below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
ABN 50 008 422 348
38-42 Wharf Road
West Ryde NSW 2114

POISON SCHEDULE OF THE MEDICINE

S4 (Prescription only medicine)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

8 January 1998

DATE OF MOST RECENT AMENDMENT

09 December 2016

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