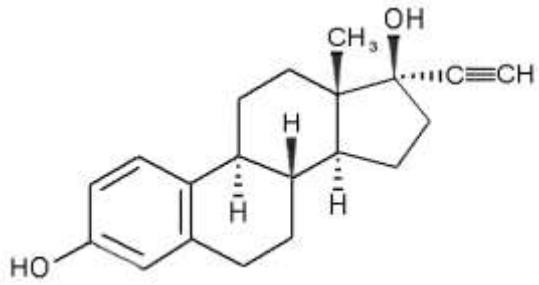
PRODUCT INFORMATION

NORDETTE® TABLETS

NAME OF THE MEDICINE

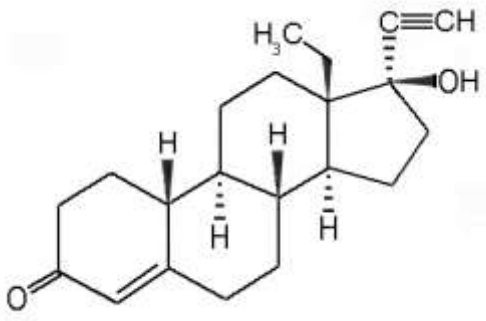
Levonorgestrel and Ethinylestradiol

Chemically, ethinylestradiol is 19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol and has the following structure: -



Chemical Formula:	$C_{20}H_{24}0_2$
Molecular Weight:	296.41
Melting Point:	181-185°C
CAS No:	[57-63-6]

Chemically, levonorgestrel is (-)-13β-Ethyl-17β-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one and has the following structure: -



Chemical Formula:	$C_{21}H_{28}0_2$
Molecular Weight:	312.45
Melting Point:	232-239°C
CAS No:	[797-63-7]

DESCRIPTION

Ethinylestradiol is a white to creamy white, odourless, crystalline powder. It is insoluble in water and soluble in alcohol, chloroform, ether, vegetable oils, and aqueous solutions of alkali hydroxides.

Levonorgestrel is a white crystalline powder that is very slightly soluble in water, slightly soluble in alcohol and acetone, and soluble in chloroform.

Each NORDETTE package contains 28 tablets; 21 active white tablets of which each contain 30 micrograms ethinylestradiol and 150 micrograms levonorgestrel, and 7 red inert tablets.

Each tablet contains the following excipients: calcium carbonate, glycol montanate (red tablet only), macrogol 6000, magnesium stearate, sucrose, maize starch, povidone, white beeswax

(white tablet only), carnauba wax (white tablet only), purified talc and lactose monohydrate. The red inactive tablets contain the colourants erythrosine and brilliant scarlet 4R.

PHARMACOLOGY

The hormonal components of NORDETTE inhibit ovulation by suppressing gonadotropin release. Secondary mechanisms, which may contribute to the effectiveness of NORDETTE as a contraceptive, include changes in the cervical mucus (which increase the difficulty of sperm penetration) and changes in the endometrium (which reduce the likelihood of implantation).

Pharmacokinetics

Ethinylestradiol and levonorgestrel are rapidly and almost completely absorbed from the gastrointestinal tract. Ethinylestradiol is subject to considerable first-pass metabolism with a mean bioavailability of 40-45%. Levonorgestrel does not undergo first-pass metabolism and is therefore completely bioavailable.

Levonorgestrel is extensively plasma protein bound both to sex hormone binding globulin (SHBG) and albumin. Ethinylestradiol, however, is bound in plasma only to albumin and enhances the binding capacity of SHBG. Following oral administration, peak plasma levels of each drug occur within 1 to 4 hours.

The elimination half-life for ethinylestradiol is approximately 25 hours. It is primarily metabolised by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed, and these are present both free and as conjugates with glucuronide and sulphate. Conjugated ethinylestradiol is excreted in bile and subject to enterohepatic recirculation. About 40% of the drug is excreted in the urine and 60% is eliminated in the faeces.

The elimination half-life for levonorgestrel is approximately 24 hours. The drug is primarily metabolised by reduction of the A ring followed by glucuronidation. About 60% of levonorgestrel is excreted in the urine and 40% is eliminated in the faeces.

INDICATIONS

NORDETTE is indicated for the prevention of pregnancy.

CONTRAINDICATIONS

NORDETTE 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 NORDETTE use, the product should be stopped immediately.

- Presence or risk of venous thromboembolism (VTE) (see PRECAUTIONS);
  - A history of or current deep vein thrombosis, or thromboembolic disorders;
  - 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 or history of ATE (e.g. myocardial infarction or stroke) or prodromal condition (e.g. angina pectoris or transient ischaemic attack [TIA]) or thrombogenic valvulopathies or thrombogenic rhythm disorders;
  - Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (e.g. anticardiolipin-antibodies and lupus anticoagulant);
  - Headaches with focal neurological symptoms (such as aura) including hemiplegic migraine;
  - 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 involvement;
    - Uncontrolled hypertension;
    - Severe dyslipoproteinaemia;
    - Sickle cell anaemia.
- Pancreatitis or a history thereof if associated with severe hypertriglyceridemia;
- Presence or history of active hepatic disease as long as liver function values have not returned to normal;
- Presence or history of liver tumours (benign or malignant);
- Known or suspected sex steroid-influenced malignancies (e.g. of the genital organs or the breasts);
- Undiagnosed vaginal bleeding;
- Known or suspected pregnancy;
- Combined oral contraceptives (COCs) are contraindicated for concomitant use with certain anti-viral hepatitis C virus (HCV) medicinal products such as ombitasvir, paritaprevir, ritonavir and dasabuvir (see **PRECAUTIONS, Hepatic Neoplasia/Liver Disease/Hepatitis C** and **INTERACTIONS WITH OTHER MEDICINES**);
- Hypersensitivity to any of the ingredients contained in NORDETTE.

PRECAUTIONS

In the absence of the above contraindications, if any of the conditions/risk factors mentioned below are present, the benefits of NORDETTE 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 NORDETTE should be discontinued.

Circulatory Disorders

Epidemiological studies have suggested an association between the use of COCs containing ethinylestradiol and an increased risk of venous and arterial thrombotic and thromboembolic events, such as myocardial infarction, stroke, deep venous thrombosis, and pulmonary embolism. These events occur rarely in average-risk women.

For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient.

Venous Thrombosis and Thromboembolism

The physician should be alert to the earliest manifestations of those disorders (e.g. pulmonary embolism, cerebrovascular insufficiency, cerebral haemorrhage, cerebral thrombosis, coronary occlusion, retinal thrombosis, mesenteric thrombosis). Should any of these occur or be suspected, the medicine should be discontinued immediately.

Risk of Venous thromboembolism (VTE)

The use of any COC increases the risk of VTE compared with no use. The women considering using NORDETTE should 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.

The risk of VTE with the COC is greatest for products containing over 50 µg of ethinylestradiol. There is less risk for products such as NORDETTE containing less than 35 µg ethinylestradiol. Products that contain the progestagens levonorgestrel, norgestimate or norethisterone are associated with the lowest risk of VTE.

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 sensitivity 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.

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.

However 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, cerebral, 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).

NORDETTE 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

The risk of venous thrombotic and thromboembolic events is further increased in women with conditions predisposing for venous thrombosis and thromboembolism. Examples of predisposing conditions for venous thrombosis and thromboembolism are:

- 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;
- Recent delivery or second trimester abortion.

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 NORDETTE (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 NORDETTE 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.

The increased risk of VTE during the postpartum period should be considered if re-starting NORDETTE. Since the immediate post-partum period is associated with an increased risk of thromboembolism, combined oral contraceptives should be started no earlier than day 28 after delivery in a non-lactating woman, or second-trimester abortion.

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.

Arterial Thrombosis and Thromboembolism

Risk of arterial thromboembolism (ATE)

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

The risk of arterial thrombotic and thromboembolic complications in COC users further increases in women with risk factors. NORDETTE 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

Caution must be exercised when prescribing COCs for women with risk factors for arterial thrombotic and thromboembolic events, such as:

- Increasing age, particularly above 35 years;
- Smoking;
- Hypertension;
- Hyperlipidaemias;
- 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;
- History of pre-eclamptic toxaemia.

Cigarette smoking increases the risk of serious cardiovascular adverse reactions from COC use. This risk increases with age and with the extent of smoking (in epidemiology studies, smoking 15 or more cigarettes per day was associated with a significantly increased risk), and is quite marked in women over 35 years of age. 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).

The onset or exacerbation of migraine or development of headache of a new pattern that is recurrent, persistent, or severe requires discontinuation of the medicine and evaluation of the cause. Women with migraine (particularly migraine with aura) who take combined oral contraceptives may be at increased risk of stroke.

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.

Medical examination/consultation

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of COC use, guided by the contraindications and precautions, and should be repeated at least annually during the use of COCs. Pregnancy should be ruled out before the start of therapy. Baseline and periodic blood glucose determinations should be performed in patients predisposed to diabetes mellitus. A Papanicolaou (Pap) smear should be performed if the patient has been sexually active or if it is otherwise indicated. Periodic medical assessment is also of importance because contraindications (e.g. a transient ischaemic attack, etc.) or risk factors (e.g. a family history of venous or arterial thrombosis) may appear for the first time during the use of a COC. The frequency and nature of these assessments should be adapted to the individual woman but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests.

The woman should also be instructed to carefully read the user leaflet and to adhere to the advice given.

Ocular Lesions

With use of combined oral contraceptives, there have been reports of retinal vascular thrombosis, which may lead to partial or complete loss of vision. Discontinue oral contraceptives and institute appropriate diagnostic and therapeutic measures if there is unexplained, gradual or sudden, partial or complete loss of vision; proptosis or diplopia; papilloedema; or any evidence of retinal vascular lesions or optic neuritis.

Elevated Blood Pressure

An increase in blood pressure has been reported in patients receiving oral contraceptives.

In women with hypertension, or a history of hypertension or hypertension related diseases; another method of contraception may be preferable. If combined oral contraceptives are used in such cases, close monitoring is recommended and, if a significant increase in blood pressure occurs, the drug should be discontinued. Combined oral contraceptives are contraindicated in women with uncontrolled hypertension.

In some women, hypertension may occur within a few months of beginning use. In the first year of use, the prevalence of women with hypertension is low but the incidence increases with increasing exposure. Age is also strongly correlated with the development of hypertension in oral contraceptive users. Women who previously have had hypertension during pregnancy may be more likely to develop an elevation of blood pressure when given oral contraceptives. If blood

pressure rises markedly, the drug should be discontinued. Hypertension that develops as a result of taking oral contraceptives usually returns to normal after discontinuing the drug.

Carcinoma of the Reproductive Organs

Cervical Cancer

The most important risk factor for cervical cancer is persistent human papillomavirus infection.

Several epidemiological studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia or invasive cervical cancer. The studies suggest that there is an "ever used" effect in addition to duration of use. These findings must be balanced against evidence of effects attributable to sexual behaviour, smoking and other factors. In cases of undiagnosed abnormal genital bleeding, adequate diagnostic measures are indicated.

Breast Cancer

A meta-analysis from 54 epidemiological studies showed 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 compared to never-users. The increased risk gradually disappears during the course of the 10 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 contraceptive users is small in relation to the lifetime 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 contraceptive users (due to more regular clinical monitoring), the biological effects of combined oral contraceptives or a combination of both. Breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

Established risk factors for the development of breast cancer include increasing age, family history, obesity, nulliparity, and late age for first full-term pregnancy.

Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver.

In all cases of undiagnosed, persistent, or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to eliminate the possibility of 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.

Hepatic Neoplasia/Liver Disease/Hepatitis C

In very rare cases hepatic adenomas, and in extremely rare cases, hepatocellular carcinoma may be associated with combined oral contraceptive use. Hepatic adenomas may rupture and cause death through intra-abdominal haemorrhage. The risk appears to increase with duration of combined oral contraceptive use. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen and should be considered if the patient has abdominal pain and tenderness or evidence of intra-abdominal bleeding.

Cholestatic jaundice has been reported in users of oral contraceptives. If this occurs, the drug should be discontinued. Women with a history of cholestasis during pregnancy or combined oral contraceptive-related cholestasis are more likely to have this condition with combined oral contraceptive use. If these patients receive a combined oral contraceptive they should be carefully monitored and, if the condition recurs, the combined oral contraceptive should be discontinued.

Hepatocellular injury has been reported with combined oral contraceptive use. Early identification of drug-related hepatocellular injury can decrease the severity of hepatotoxicity when the drug is discontinued. If hepatocellular injury is diagnosed, patients should stop their combined oral contraceptive use, use a non-hormonal form of contraception and consult their doctor.

Acute or chronic disturbances of liver function require the discontinuation of combined oral contraceptive use until liver function has returned to normal (see **CONTRAINDICATIONS**).

Steroid hormones may be poorly metabolised in patients with impaired liver function and should be administered with caution to such patients.

Hepatitis C

During clinical trials with patients treated for HCV infections with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequently in women using ethinylestradiol-containing medications such as COCs (see **CONTRAINDICATIONS** and **INTERACTIONS WITH OTHER MEDICINES**).

Gallbladder Disease

Studies report an increased risk of surgically confirmed gallbladder disease in users of estrogens and oral contraceptives. Combined oral contraceptives may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women.

Angioedema

Exogenous estrogens may induce or exacerbate symptoms of angioedema, particularly in women with hereditary angioedema.

Carbohydrate and Lipid Metabolic Effects

Glucose intolerance has been reported in combined oral contraceptive users. Women with impaired glucose tolerance or diabetes mellitus who used combined oral contraceptives should be carefully monitored.

A small proportion of women will have adverse lipid changes while taking oral contraceptives. Non-hormonal contraception should be considered in women with uncontrolled dyslipidaemias.

Persistent hypertriglyceridaemia may occur in a small proportion of combined oral contraceptive users. Elevations of plasma triglycerides in combined oral contraceptive users may lead to pancreatitis and other complications.

Estrogens increase serum high-density lipoproteins (HDL cholesterol), whereas a decline in serum HDL cholesterol has been reported with many progestational agents. Some progestins may elevate low-density lipoprotein (LDL) levels and may render the control of hyperlipidaemias more difficult. The net effect of a COC depends on the balance achieved between doses of estrogen and progestin and the nature and absolute amount of progestins used in the contraceptive. The amount of both hormones should be considered in the choice of a COC.

Women who are being treated for hyperlipidaemias should be followed closely if they elect to use combined oral contraceptives.

Genital Bleeding

In some women withdrawal bleeding may not occur during the inactive-tablet interval. If NORDETTE has not been taken according to directions prior to the first missed withdrawal bleed, or if two consecutive withdrawal bleeds are missed, tablet taking should be discontinued and a non-hormonal back-up method of contraception should be used until the possibility of pregnancy is excluded.

Breakthrough bleeding, spotting and amenorrhoea are frequent reasons for patients discontinuing oral contraceptives. Breakthrough bleeding/spotting may occur in women taking NORDETTE, especially during the first three months of use. If this bleeding persists or recurs, as in all cases of irregular bleeding from the vagina, non-functional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, appropriate diagnostic measures are indicated to rule out pregnancy, infection, malignancy or other conditions. If pathology has been excluded, continuation of NORDETTE or a change to another formulation may solve the problem. Changing to a regimen with a higher estrogen content, while potentially useful in minimising menstrual irregularity should be done only if necessary, since this may increase the risk of thromboembolic disease.

Women with a history of oligomenorrhoea or secondary amenorrhoea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrhoeic after discontinuation of oral contraceptives. Women with these pre-existing problems should be advised of this possibility and encouraged to use other methods of contraception. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities.

Depression

Oral contraceptives may cause depression. Patients with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while taking oral contraceptives should stop the medication and use an alternative method of contraception in an attempt to determine whether the symptom is drug-related.

Vomiting and/or Diarrhoea

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

Other

Under the influence of estrogen-containing oral contraceptives, pre-existing uterine leiomyomata may increase in size.

These agents may cause some degree of fluid retention. Women with cardiac or renal dysfunction, convulsive disorders, migraine, or asthma require careful observation since these conditions may be exacerbated by the fluid retention which may occur in users of oral contraceptives.

Users of oral contraceptives may have disturbances in normal tryptophan metabolism, which may result in a relative pyridoxine deficiency. The clinical significance of this is yet to be determined.

Serum folate levels may be depressed by oral contraceptive use. Women who became pregnant shortly after discontinuing these drugs may have a greater chance of developing folate deficiency and its complications.

Patients should be counselled that this product does not protect against HIV infection (AIDS) or other sexually transmitted diseases.

Use During or Immediately Preceding Pregnancy

Category B3:

Pregnancy must be excluded before starting NORDETTE. If pregnancy occurs during use of NORDETTE, the preparation must be withdrawn immediately.

Oral contraceptives have not been shown to have any deleterious effects on the fetus or to increase the incidence of miscarriage in women who discontinue their use prior to conception. However, in women who discontinue oral contraceptives with the intent of becoming pregnant, a non-hormonal method of contraception is recommended for three months before attempting to conceive.

Animal studies have shown that high doses of progestogens can cause masculinisation of the female fetus. The results of these experiments in animals do not seem to be relevant to humans because of the low doses used in oral contraceptives.

Studies do not suggest a teratogenic effect when oral contraceptives are taken inadvertently during early pregnancy.

Female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective for these uses.

The administration of progestogen-only or estrogen-progestogen combinations to induce withdrawal bleeding should not be used as a test for pregnancy.

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

The increased risk of VTE during the postpartum period (recent delivery or second trimester abortion) should be considered when re-starting NORDETTE.

Use in Lactation

Estrogen-containing oral contraceptives given in the postpartum period may interfere with lactation. There may be a decrease in the quantity and a change in the composition of the breast milk. Furthermore, small amounts of contraceptive steroids and/or metabolites been identified in the milk of mothers receiving them. A few adverse effects on the child have been reported, including jaundice and breast enlargement. The use of estrogen-containing oral contraceptives should be deferred until the infant has been completely weaned.

Paediatric Use

Safety and efficacy of combined oral contraceptives have been established in women of reproductive age. Use of these products before menarche is not indicated.

Use in the Elderly

Combined oral contraceptives are not indicated for use in postmenopausal women.

Laboratory Test Interactions

Estrogen-containing preparations affect the following blood components, endocrine and liver function tests:

1. Increased prothrombin and Factors VII, VIII, IX, and X; decreased antithrombin 3; increased noradrenaline-induced platelet aggregability;

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

3. Decreased pregnanediol excretion;

4. Reduced response to metyrapone test;

5. Increased sulphobromophthalein retention.

The results of these tests should not be regarded as reliable until oral contraceptives use has been discontinued for 1-2 months. Abnormal tests should then be repeated.

Oral contraceptives may produce false positive results when neutrophil alkaline phosphatase activity is evaluated for the early diagnosis of pregnancy.

INTERACTIONS WITH OTHER MEDICINES

Interactions between ethinylestradiol and other substances may lead to decreased or increased ethinylestradiol concentrations, respectively.

Concomitant use with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin may increase the risk of ALT elevations (see **CONTRAINDICATIONS** and **PRECAUTIONS: Hepatic Neoplasia/Liver Disease/Hepatitis C**).

Therefore, COC users must switch to an alternative method of contraception (e.g., progestogen-only contraception or non-hormonal methods) prior to starting therapy with anti-viral HCV medicinal products such as ombitasvir, paritaprevir, ritonavir, dasabuvir. COCs can be restarted 2 weeks following completion of treatment with an anti-viral HCV medicinal product.

Decreased ethinylestradiol serum concentrations may cause an increased incidence of breakthrough bleeding and menstrual irregularities and may possibly reduce efficacy of the oral contraceptive.

Examples of substances that may decrease serum ethinylestradiol concentrations include:

- Any substance that reduces gastrointestinal transit time and, therefore, ethinylestradiol absorption.

- Substances that induce hepatic microsomal enzymes, such as rifampicin, phenytoin, primidone, rifabutin, dexamethasone, griseofulvin, topiramate, some protease inhibitors, modafinil, ritonavir and barbiturates.

- St. John's wort (*Hypericum perforatum*) may induce hepatic microsomal enzymes, which theoretically may result in reduced efficacy of oral contraceptives. This may also result in breakthrough bleeding.

- Certain antibiotics including ampicillin, other penicillins and tetracyclines may reduce the efficacy of oral contraceptives by decreasing enterohepatic circulation of estrogens.

During concomitant use of NORDETTE and substances that may lead to decreased ethinylestradiol serum concentrations, it is recommended that a non-hormonal back-up method of contraception (other than the rhythm or temperature methods) be used in addition to the regular intake of NORDETTE. In the case of prolonged use of such substances combined oral contraceptives should not be considered the primary contraceptive.

After discontinuation of substances that may lead to decreased ethinylestradiol serum concentrations, use of a non-hormonal back-up method of contraception is recommended for at least 7 days.

Longer use of a non-hormonal back-up method, a minimum of 4 weeks, is advisable after discontinuation of substances such as rifampicin that have led to induction of hepatic microsomal enzymes, resulting in decreased ethinylestradiol serum concentrations. It may sometimes take several weeks until enzyme induction has completely subsided, depending on dosage, duration of use and rate of elimination of the inducing substance.

Examples of substances that may increase ethinylestradiol concentrations include:

- Atorvastatin,
- Competitive inhibitors for sulphation in the gastrointestinal wall, such as ascorbic acid (vitamin C) and paracetamol.

Substances that inhibit cytochrome P4503A4 isoenzymes such as indinavir and fluconazole.

Increased intermenstrual bleeding and occasional pregnancies have been reported during concomitant administration of oral contraceptives and ampicillin, phenoxymethyl penicillin and other penicillins, sulphamethoxypyridazine, chloramphenicol, nitrofurantoin, tetracycline and neomycin. The mechanism appears to be reduced enterohepatic circulation of sex steroids due to change in bowel flora. It may be prudent for women to use supplemental forms of contraception during therapy with these antibiotics.

Oral contraceptives have been reported to antagonise the effectiveness of antihypertensive agents, anticonvulsants, oral anticoagulants, and hypoglycaemic agents. Patients should be carefully monitored for a decreased response to these drugs.

Ethinylestradiol may interfere with the metabolism of other drugs by inhibiting hepatic microsomal enzymes, or by inducing hepatic drug conjugation, particularly glucuronidation. Accordingly, plasma and tissue concentrations may either be increased e.g. cyclosporin, theophylline, corticosteroids) or decreased (e.g. lamotrigine).

Oral contraceptives may alter the effectiveness of other drugs such as phenothiazines, beta-adrenergic antagonists, tricyclic antidepressants, and caffeine, by either potentiating/enhancing their pharmacological effects or by decreasing their clearance.

Oral contraceptives may interfere with the oxidative metabolism of diazepam and chlordiazepoxide, resulting in plasma accumulation of the parent compound. Patients receiving these benzodiazepines on a long-term basis should be monitored for increased sedative effects.

The effects of benzodiazepines on oral contraceptive metabolism have not been determined.

The prescribing information of concomitant medications should be consulted to identify potential interactions.

ADVERSE EFFECTS

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

Adverse reactions are listed in the Table per CIOMS frequency categories:

Very common:	≥10%
Common:	≥1% and <10%
Uncommon:	≥0.1% and <1%
Rare:	≥0.01% and <0.1%
Very rare:	<0.01%.

Use of combined oral contraceptives has been associated with an increased risk of the following:

* Arterial and venous thrombotic and thromboembolic events, including myocardial infarction, stroke, transient ischaemic attack, venous thrombosis and pulmonary embolism;
* Cervical intraepithelial neoplasia and cervical cancer;
* Breast cancer diagnosis;
* Benign hepatic tumours (e.g. focal nodular hyperplasia, hepatic adenomas).

The following have also been reported and are believed to be drug-related:

System Organ Class	***Adverse Reaction***
Infections and Infestations	
Common	Vaginitis, including candidiasis
Neoplasms benign, malignant, and unspecified	
Very Rare	Hepatic adenomas; hepatocellular carcinomas
Immune System Disorders	
Rare	Anaphylactic/anaphylactoid reactions, including very rare cases of urticaria, angioedema and severe reactions with respiratory and circulatory symptoms
Very Rare	Exacerbation of systemic lupus erythematosus
Metabolism and Nutrition Disorders	
Uncommon	Changes in appetite (increase or decrease)
Rare	Glucose intolerance
Very Rare	Exacerbation of porphyria
Psychiatric Disorders	
Common	Mood changes, including depression; changes in libido
Nervous System Disorders	
Very Common	Headache, including migraines
Common	Nervousness; dizziness
Very Rare	Exacerbation of chorea
Eye Disorders	
Rare	Intolerance to contact lenses

System Organ Class	*Adverse Reaction*
Very Rare	Optic neuritis*; retinal vascular thrombosis
Vascular Disorders	
Very Rare	Aggravation of varicose veins
Gastrointestinal Disorders	
Common	Nausea; vomiting; abdominal pain
Uncommon	Abdominal cramps; bloating
Very Rare	Pancreatitis; ischaemic colitis
Unknown	Inflammatory bowel disease (Crohn's disease, ulcerative colitis)
Hepato-Biliary Disorders	
Rare	Cholestatic jaundice
Very Rare	Gallbladder disease, including gallstones**
Unknown	Hepatocellular injury (e.g. hepatitis, hepatic function abnormal)
Skin and Subcutaneous Tissue Disorders	
Common	Acne
Uncommon	Rash (allergic); chloasma (melasma), which may persist; hirsutism; alopecia
Rare	Erythema nodosum
Very Rare	Erythema multiforme
Renal and Urinary Disorders	
Very Rare	Haemolytic uraemic syndrome
Reproductive System and Breast Disorders	
Very Common	Metrorrhagia (Breakthrough bleeding/spotting)
Common	Breast pain, tenderness, enlargement, secretion; dysmenorrhoea; change in menstrual flow; change in cervical ectropion and secretion; amenorrhoea
General Disorders and Administration Site Conditions	
Common	Fluid retention/oedema
Investigations	
Common	Changes in weight (increase or decrease)
Uncommon	Increase in blood pressure; changes in serum lipid levels, including hypertriglyceridaemia

System Organ Class	*Adverse Reaction*
Rare	Decrease in serum folate levels.***

* Optic neuritis may lead to partial or complete loss of vision;

** Combined oral contraceptives may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women;

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

The following adverse reactions have been reported in users of oral contraceptives, but the association has been neither confirmed nor refuted:

Change in corneal curvature (steepening), Premenstrual-like syndrome, Cataracts, Haemorrhagic eruption, Cystitis-like syndrome, Megaloblastic Anaemia, Budd-Chiari Syndrome.

DOSAGE AND ADMINISTRATION

How to take NORDETTE

Each package of NORDETTE contains 21 white active tablets and 7 red inactive tablets. To achieve maximum contraceptive effectiveness, NORDETTE must be taken as directed and at intervals not exceeding 24 hours. Women should be instructed to take the tablets at the same time every day, preferably after the evening meal or at bedtime.

How to Start NORDETTE

No Preceding Hormonal Contraceptive Use (in the Past Month)

On the first day of the menstrual cycle, i.e. the first day of bleeding, the woman will take the first white active tablet corresponding to that day of the week from the green shaded section of the NORDETTE package. Thereafter, one white active tablet is taken daily, following the arrows on the package, until all 21 white active tablets have been taken. The woman should then be instructed to take one red inactive tablet from the light shaded section of the NORDETTE pack daily for the next seven days following the arrows marked. Withdrawal bleeding should usually occur within 3 days after the last white active tablet is taken and may not have finished before the next pack is started.

During this first cycle, a non-hormonal back-up method of contraception (other than the rhythm or temperature methods) should be used until one white active tablet has been taken daily for 7 consecutive days. If the white active tablets are started after Day 5, it must be considered that ovulation and conception may have occurred before the tablets were started.

The next and all subsequent courses will begin on the day after the last package was completed, even if withdrawal bleeding has not occurred or is still in progress. Each course of NORDETTE is thus begun on the same day of the week as the first course, with a white active tablet from the

green shaded section of the package. If withdrawal bleeding does not occur and NORDETTE has been taken according to directions, it is unlikely that the woman has conceived. She should be instructed to begin a second course of NORDETTE on the usual day. If bleeding does not occur at the end of this second cycle, NORDETTE should not be taken until diagnostic procedures to exclude the possibility of pregnancy have been performed.

If the patient has not adhered to the prescribed regimen (missed one or more 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 NORDETTE is resumed.

Changing from another Combined Oral Contraceptive

Women changing from another combined oral contraceptive product should start NORDETTE on the day after the last active tablet of her previous combined oral contraceptive, by taking the first white active tablet corresponding to that day of the week from the green shaded section of the package. This will shorten the last cycle of the previous combined oral contraceptive, and may prevent or reduce withdrawal bleeding at the end of that cycle. The first cycle with NORDETTE may also be shorter.

During the first NORDETTE cycle, a non-hormonal back-up method of contraception (other than the rhythm or temperature methods) should be used until one white active tablet has been taken daily for 7 consecutive days.

If transient spotting or breakthrough bleeding occurs, 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.

Changing from a Progestogen Only Method (Progestogen-Only Tablet, Injection, Implant)

Women may switch any day from the progestogen-only tablet and should begin NORDETTE the next day. She should start NORDETTE on the day of an implant removal or, if using an injection, the day the next injection would be due. In all these situations, women should be advised to use a non-hormonal back-up method of contraception (other than the rhythm or temperature methods) until one white active tablet has been taken daily for 7 consecutive days.

Following First-Trimester Abortion

Women may start NORDETTE immediately. Additional contraceptive measures are not needed.

Following Delivery or Second-Trimester Abortion

Since the immediate post-partum period is associated with an increased risk of thromboembolism, combined oral contraceptives should be started no earlier than day 28 after delivery in the non-lactating mother or after second trimester abortion. Women should be advised to use a non-hormonal back-up method of contraception (other than the rhythm or temperature methods) until one white active tablet has been taken daily for 7 consecutive days. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of combined oral contraceptive use or the woman must wait for her first menstrual period.

Management of Missed Tablets

Contraceptive efficacy may be reduced if active tablets are missed and particularly if the missed tablets extend the inactive tablet interval.

If one white active tablet is missed, but is less than 12 hours late, it should be taken as soon as it is remembered. Subsequent tablets should be taken at the usual time.

If one white active tablet is missed, and is more than 12 hours late, or if two white active tablets are missed, contraceptive protection may be reduced. The last missed tablet should be taken as soon as it is remembered, even if this means taking two tablets in one day. Subsequent tablets should be taken at the usual time. In addition, a non-hormonal back-up method of contraception (other than the rhythm or temperature methods) should be used until one white active tablet has been taken daily for 7 consecutive days.

If the 7 days where back up is required run beyond the last white active tablet in the current pack, the next pack must be started on the day following the intake of the last white active tablet in the current pack; all inactive (red) tablets should be discarded. This prevents an extended break in tablet taking of active tablets that may increase the risk of escape ovulation. The woman is unlikely to have a withdrawal bleed until the inactive-tablet interval of the second pack, but she may experience spotting or breakthrough bleeding on days when active tablets are taken. If the woman does not have a withdrawal bleed at the end of the second pack, the possibility of pregnancy must be ruled out before resuming tablet taking.

If the woman misses one or more inactive (red) tablets, she is still protected against pregnancy, provided she begins the white active tablets on the proper day.

If three consecutive white active tablets are missed, NORDETTE should be discontinued and the remainder of the package discarded. A new package should be started on the eighth day after the last tablet was taken. A non-hormonal back up method of contraception (other than the rhythm or temperature methods) should be used until one white active tablet has been taken daily for 7 consecutive days.

If withdrawal bleeding does not occur and NORDETTE has been taken according to directions, it is unlikely that the woman has conceived. She should be instructed to begin a second course of NORDETTE on the usual day. If bleeding does not occur at the end of this second cycle, NORDETTE should not be taken until diagnostic procedures to exclude the possibility of pregnancy have been performed.

If the patient has not adhered to the prescribed regimen (missed one or more 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 NORDETTE is resumed.

Vomiting or Diarrhoea

If vomiting occurs within 4 hours after tablet taking, absorption may not be complete. In such an event, the advice concerning Management of Missed Tablets is applicable. The woman must take the extra active tablet(s) needed from a backup pack. Diarrhoea may increase gastrointestinal motility and reduce hormone absorption.

OVERDOSAGE

Symptoms of oral contraceptive overdosage in adults and children may include nausea, vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue; withdrawal bleeding may occur in females. There is no specific antidote and further treatment of overdose, if necessary, is directed to the symptoms.

PRESENTATION AND STORAGE CONDITIONS

NORDETTE tablets are presented in PVC/aluminium blister. The blistered product is placed in an aluminium pouch with a silica gel desiccant.

One month pack containing one blister#; four month pack containing 4 blisters.

Each blister contains 21 white tablets each containing ethinylestradiol 30 micrograms and levonorgestrel 150 micrograms, and 7 red inert tablets.

Not currently marketed in Australia.

Storage Conditions

Store below 25ºC.

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

24 July 2008.

DATE OF MOST RECENT AMENDMENT

12 January 2018.

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