

AUSTRALIAN PRODUCT INFORMATION

NORINYL-1[®] 28 DAY

(NORETHISTERONE AND MESTRANOL)

TABLETS

1. NAME OF THE MEDICINE

Norethisterone and Mestranol

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each white active tablet contains norethisterone 1 mg and mestranol 50 µg.

Each orange tablet is a placebo tablet.

Excipients with known effect

White tablets: Lactose monohydrate

Orange tablets: Lactose, Lactose monohydrate

For the full list of excipients, see section 6.1, List of Excipients.

3. PHARMACEUTICAL FORM

Tablets.

Each NORINYL-1 28 Day blister pack contains 21 white active tablets and 7 orange placebo tablets.

The white active tablets are round, flat tablets with bevelled edges, approximately 3/16 inches diameter, engraved Searle on one side and 1 on the other. The orange inert tablets are round flat with bevelled edges, approximately 3/16 inches in diameter, engraved Searle on one side and P on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral Contraception.

NORINYL-1 is an agent for conception control.

4.2 Dose and method of administration

To achieve maximum contraceptive effectiveness, NORINYL-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 NORINYL-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 active tablet has been taken. The woman should be advised that her first cycle after taking all NORINYL-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 NORINYL-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 NORINYL-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.

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

Changing From Another Pill: If a woman is switching to NORINYL-1 28 day from another 28 day oral contraceptive pack, then all tablets in the current 28 day pack should be finished and NORINYL-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 NORINYL-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 NORINYL-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 NORINYL-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 NORINYL-1 28 day cycle, until seven consecutive white active tablets have been taken.

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.

NORINYL-1 28 day can be prescribed postpartum for the non-lactating mother or postabortion 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 NORINYL-1 28 day must be initiated by the 12th (but not before the 7th) day postpartum, or immediately postabortion 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 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 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 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 NORINYL-1 28 day is resumed. In the case of the continuous intake of active tablets from two packs of NORINYL-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 NORINYL-1 28 day is resumed.

Concurrent Medication: If the woman is taking other drugs that may interact with norethisterone or mestranol, she should continue to take her tablets as usual but also employ a non-hormonal 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 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 NORINYL-1 28 day. If, however, vomiting or diarrhoea occurs during or shortly after the intake of NORINYL-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 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 circumstance reducing the effectiveness of NORINYL-1 28 day is protracted, other methods of contraception should be considered.

4.3 Contraindications

NORINYL-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 the use of NORINYL-1, the product should be stopped immediately.

- Presence or risk of venous thromboembolism (VTE) (see section 4.4, Special Warnings and Precautions for Use);
 - 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 section 4.4, Special Warnings and Precautions for Use);
 - 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 (e.g. anticardiolipin-antibodies and lupus anticoagulant);
 - Headaches with focal neurological symptoms (such as aura) including haemiplegic 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 symptoms;
 - Uncontrolled hypertension;
 - Severe dyslipoproteinaemia;
 - Sick 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, 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;

- 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 section 4.4, Special Warnings and Precautions for Use, **Hepatic Neoplasia/Liver Disease/Hepatitis C** and section 4.5, Interactions With Other Medicines and Other Forms of Interactions);
- Hypersensitivity to any of the ingredients contained in NORINYL-1.

4.4 Special warnings and precautions for use

If any of the conditions/risk factors mentioned below are present, the benefits of NORINYL-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 NORINYL-1 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 NORINYL-1 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.

It is important that women understand that VTE associated with COC use is rare in average-risk women. The baseline risk for VTE increases with age, obesity and smoking. 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 ethinylestradiol. Products containing less than 35 µg of ethinylestradiol have a lower risk. It is unknown how the risk of mestranol compares to this. Of the progestagens available, norethisterone is 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.

Risk1 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.

The increased risk of VTE during the postpartum period must be considered if restarting NORINYL-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).

NORINYL-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

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 NORINYL-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 NORINYL-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.

The increased risk of VTE during the postpartum period should be considered if re-starting NORINYL-1. 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.

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. NORINYL-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

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 toxæmia.

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).

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 estrogen.

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 estrogen 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 Reproductive Organs

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

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 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.

In cases of undiagnosed abnormal genital bleeding, adequate diagnostic measures are indicated.

Breast Cancer

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.

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

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/Liver Disease/Hepatitis C

In very rare cases, hepatic adenomas, and in extremely rare cases, hepatocellular carcinoma may be associated with COC use. The risk appears to increase with duration of COC use. Rupture of hepatic adenomas may cause death through intra abdominal haemorrhage.

Indirect calculations have estimated the attributable risk of hepatic adenomas 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.

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.

Women with a history of COC-related cholestasis and women who develop cholestasis during pregnancy are more likely to develop cholestasis with COC use. Such patients who use COCs should be carefully monitored, and COC use should be discontinued if cholestasis recurs.

Hepatocellular injury has been reported with COC 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 COC, use a non-hormonal form of birth control, and consult their doctor.

Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until liver function has returned to normal (see section 4.3, Contraindications).

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 sections 4.3, Contraindications and 4.5, Interactions With Other Medicines and Other Forms of Interactions).

Ocular Lesions

With use of combined oral contraceptives, there have been clinical case reports of retinal 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; onset of proptosis or diplopia; papilledema; or any evidence of retinal vascular lesions or optic neuritis.

Gallbladder Disease

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogen. 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 estrogen 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 estrogen cause glucose intolerance with impaired insulin secretion, while lower doses of estrogen 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. Glucose intolerance has been reported in COC users. Women with impaired glucose tolerance or diabetes mellitus who use COCs should be carefully monitored (see section 4.3, Contraindications).

A small proportion of women will have adverse lipid changes while taking COCs. Non-hormonal birth control should be considered in women with uncontrolled dyslipidemias. Persistent hypertriglyceridemia may occur in a small proportion of COC users. Elevations of plasma triglycerides in COC 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 COCs.

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.

COC use is contraindicated in women with uncontrolled hypertension (see section 4.3, Contraindications).

Migraine/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.

Women with migraine (particularly migraine with aura) who take COCs may be at increased risk of stroke.

Angioedema

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

Genital Bleeding

In some women withdrawal bleeding may not occur during the inactive-tablet interval. If the COC 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 birth control should be used until the possibility of pregnancy is excluded.

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 amenorrhoea pregnancy should be ruled out.

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

Sexually Transmitted Diseases

This product (like all oral contraceptives) is intended to prevent pregnancy. Patients should be counselled that this product 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 section 4.2, Dose and Method of 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. A Papanicolaou (Pap) smear should be performed if the patient has been sexually active or if it is otherwise indicated. 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 hyperlipidaemias 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. Patients becoming significantly depressed while taking COCs should stop the medication and use an alternative method of birth control in an attempt to determine whether the symptom is drug-related.

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 estrogens 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 the Elderly

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

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.

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.

4.5 Interactions with other medicines and other forms of interactions

Ethinylestradiol is the active form of mestranol which is the estrogen contained in NORINYL-1. 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 section 4.3, Contraindications and section 4.4, Special Warnings and Precautions for Use, **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 COC.

During concomitant use of ethinylestradiol-containing products and substances that may lead to decreased ethinylestradiol serum concentrations, it is recommended that a non-hormonal back-up method of birth control (such as condoms and spermicide) be used in addition to the regular intake of NORINYL-1. In the case of prolonged use of such substances COCs 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 back-up method is advisable after discontinuation of substances 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 decrease serum ethinylestradiol concentrations:

- Any substance that reduces gastrointestinal transit time and, therefore, ethinylestradiol absorption
- Substances that induce hepatic microsomal enzymes, such as rifampicin, rifabutin, barbiturates, primidone, phenytoin, dexamethasone, griseofulvin, topiramate, some protease inhibitors, modafinil
- *Hypericum perforatum*, also known as St. John's wort, and ritonavir (possibly by induction of hepatic microsomal enzymes)
- Certain antibiotics (e.g., ampicillin and other penicillins, tetracyclines), by a decrease of enterohepatic circulation of estrogens

Reduced efficacy and increased incidence of breakthrough bleeding and menstrual irregularities have also been associated with concomitant use of carbamazepine, oxacillin and trimethoprim sulfamethoxazole.

There have been reports of pregnancy when COCs were co-administered with certain antibiotics (e.g., ampicillin and other penicillins, tetracyclines).

Examples of substances that may increase serum ethinylestradiol concentrations:

- Atorvastatin

- Competitive inhibitors for sulfation in the gastrointestinal wall, such as ascorbic acid (vitamin C) and paracetamol
- Substances that inhibit cytochrome P450 3A4 isoenzymes such as indinavir and fluconazole,

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).

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

4.6 Fertility, pregnancy and lactation

Effects on Fertility

No data available.

Use in Pregnancy

PREGNANCY CATEGORISATION: B3

If pregnancy occurs during treatment with COCs, further intake should be discontinued.

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.

4.7 Effect on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

The most serious adverse reactions associated with the use of oral contraceptives are indicated under sections 4.3, Contraindications and 4.4, Special Warnings and Precautions for Use).

Use of COCs has been associated with increased risk of the following:

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

Adverse reactions are listed below according to system organ class and the following 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%

System Organ Class	Adverse Reaction
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Cardiac disorders

Not known	Myocardial infarction
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Infections and infestations

Common	Vaginitis, including candidiasis
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Musculoskeletal and connective tissue disorders

Not known	Muscle spasms, back pain
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Neoplasms benign, malignant, and unspecified

Very Rare	Hepatocellular carcinomas
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Not known	Carcinomas, benign liver tumours
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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

Other reactions of possible immunologic origin may be listed under other organ system subheadings.

Metabolism and nutrition disorders

Uncommon	Changes in appetite (increase or decrease)
Rare	Glucose intolerance
Very Rare	Exacerbation of porphyria
Not known	Reduced tolerance to carbohydrates, vitamin B6 deficiency

Psychiatric disorders

Common	Mood changes, including depression, changes in libido
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Nervous system disorders

Very common	Headache, including migraines
Common	Nervousness, dizziness
Very Rare	Exacerbation of chorea

Eye disorders

Rare	Intolerance to contact lenses
Very Rare	Optic neuritis*, retinal vascular thrombosis
Not known	Change in corneal curvature (steepening), cataracts

Vascular disorders

Very Rare	Aggravation of varicose veins
Not known	Arterial thromboembolism, cerebral haemorrhage, cerebral thrombosis, mesenteric thrombosis, pulmonary embolism, thrombophlebitis, hypertension

Gastrointestinal disorders

Common	Nausea, vomiting, abdominal pain
Uncommon	Abdominal cramps, bloating
Very Rare	Pancreatitis, ischaemic colitis
Not known	Inflammatory bowel disease (Crohn's Disease, ulcerative colitis), dyspepsia

Hepatobiliary disorders

Rare	Cholestatic jaundice
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Very Rare	Gallbladder disease, including gallstones**
Not known	Hepatocellular injury (e.g. hepatitis, hepatic function abnormal), Budd-Chiari syndrome

Skin and subcutaneous tissue disorders

Common	Acne
Uncommon	Rash, chloasma (melasma), which may persist, hirsutism, alopecia
Rare	Erythema nodosum
Very Rare	Erythema multiforme
Not known	Loss of scalp hair, haemorrhagic eruption, photosensitivity

Renal and urinary disorders

Very Rare	Haemolytic uraemic syndrome
Not known	Impaired renal function, cystitis-like syndrome

Reproductive system and breast disorders

Very common	Breakthrough bleeding/spotting
Common	Breast pain, tenderness, enlargement, secretion; dysmenorrhoea, change in menstrual flow, change in cervical ectropion and secretion, amenorrhoea
Not known	Diminution in lactation when given immediately postpartum, temporary infertility after discontinuation of treatment, pre-menstrual syndrome

General disorders and administration site conditions

Common	Fluid retention/oedema
Not known	Fatigue

Investigations

Common	Changes in weight (increase or decrease)
Uncommon	Increase in blood pressure; changes in serum lipid levels, including hypertriglyceridemia
Rare	Decrease in serum folate levels***

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

** COCs may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women.

*** Serum folate levels may be depressed by COC therapy. This may be of clinical significance if the woman becomes pregnant shortly after discontinuing COCs.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Signs and symptoms

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 tenderness, dizziness, abdominal pain, drowsiness/fatigue and withdrawal bleeding may occur in females.

Recommended treatment

In the case of overdosage or accidental ingestion, the patient should be observed and given supportive treatment, as there is no specific antidote.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Progestin-estrogen combination products prevent ovulation by suppressing secretion of follicle-stimulating hormone (FSH) and leutinising hormone (LH). As a consequence, secretion of all ovarian steroids, including estrogen, progesterone, and androgen is also suppressed. Combination products may also exert minor direct inhibitory effects on the reproductive tract, such as altering cervical mucus to decrease sperm penetration, and decreasing the motility and secretions of the fallopian tubes and uterus.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, the absolute bioavailability of norethisterone is about 65%.

Distribution

In the plasma, about 80% of norethisterone is bound to sex hormone binding globulin and albumin. The time to peak plasma concentration ranges from 0.5 to 4 hours, being more delayed as the dose increases.

Metabolism

Norethisterone undergoes extensive first-pass metabolism.

Mestranol undergoes rapid hepatic demethylation to ethinylestradiol, its active form.

Excretion

The elimination half-life is about 5-14 hours. Norethisterone is partially eliminated, mainly as metabolites, in the faeces via biliary excretion.

Excretion of mestranol is primarily renal. The biological half-life is about 50 hours.

5.3 Preclinical safety data

Carcinogenicity

No data available.

Genotoxicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

White active tablet

Magnesium stearate,
Povidone,
Maize starch,
Lactose monohydrate.

Orange placebo tablet

Magnesium stearate,
Microcrystalline cellulose,
Lactose,

Lactose monohydrate,
Sunset yellow FCF.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Stored below 25°C.

6.5 Nature and contents of container

NORINYL-1 28 day tablets are presented in PVC/aluminium blister.

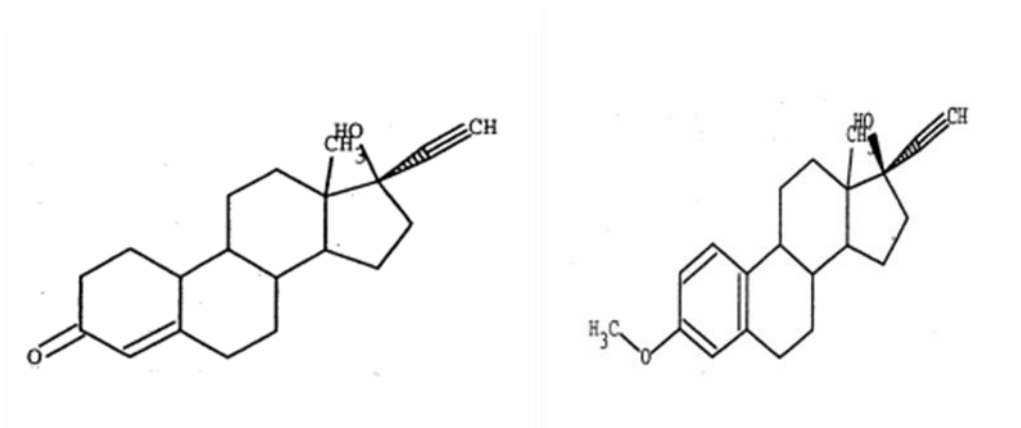
Four month pack contains four blisters.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Chemical structure



CAS number

Norethisterone

Mestranol

CAS: 68-22-4

CAS: 72-33-3

Norethisterone is a white or yellowish white crystalline powder. It is practically insoluble in water, soluble in chloroform, and slightly soluble in ethanol (96%).

Mestranol is a white or almost white, crystalline powder. It is practically insoluble in water, freely soluble in chloroform, soluble in acetone, in 1,4-dioxan and in ether, and sparingly soluble in ethanol (96%).

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription only medicine)

8. SPONSOR

Pfizer Australia Pty Ltd

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Toll Free Number: 1800 675 229
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

7 November 1997

10. DATE OF REVISION

11 October 2018.

® Registered trademark

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Reformat PI to SPC format
Section 4.5	Revision of information related to interaction between combined oral contraceptives and antibiotics