

DATA SHEET

NAME OF MEDICINE

NORINYL-1 (21 day pack)

21 norethisterone 1 mg and mestranol 0.05 mg tablets.

NORINYL-1 28 (28 day pack)

21 norethisterone 1 mg and mestranol 0.05 mg tablets and 7 inert lactose tablets.

PRESENTATION

Norethisterone 1 mg and mestranol 0.05 mg tablets are white, round, flat with bevelled edges, 3/16" in diameter and engraved 'SEARLE' on one side and '1' on the reverse. Inert lactose tablets are orange, round, flat with bevelled edges, 3/16" in diameter and engraved 'SEARLE' on one side, and 'P' on the other.

USES

Actions

Like other combination type pills, NORINYL-1 produces a contraceptive effect primarily by suppressing the hypothalamic pituitary system resulting in prevention of ovulation. The oestrogenic compound, mestranol, acts by suppressing secretion of follicle stimulating hormone (FSH), resulting in prevention of follicle development and the rise of plasma oestradiol which is thought to be the stimulus for releasing luteinising hormone (LH). The progestogenic compound, norethisterone, primarily acts by inhibiting the preovulatory rise of LH.

Long-term administration of combination type oral contraceptives may also produce a direct effect on ovarian steroidogenesis or the response of the ovary to gonadotrophins. Although the primary mechanism of action is inhibition of ovulation, alterations in the genital tract including changes in the cervical mucus (which increases the difficulty of sperm penetration) and the endometrium (which reduce the likelihood of implantation) may also contribute to contraceptive effectiveness.

Pharmacokinetics

Both norethisterone and mestranol are rapidly absorbed from the gastrointestinal tract. Following oral administration, metabolites of both compounds appear in the urine as conjugated glucuronides and sulfates, with unconjugated metabolites appearing in the faeces.

Indications

Oral contraception. NORINYL-1 is primarily designed as an agent for conception control, however, it is also useful in the treatment of certain menstrual disorders. If menstrual periods are heavy, irregular or painful, treatment with NORINYL-1 may prove beneficial.

DOSAGE AND ADMINISTRATION

21 DAY PACK

Norinyl-1 21 Day Pack

To achieve maximum contraceptive effectiveness, Norinyl-1 21 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 everyday, 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 Norinyl-1 21 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 a seven day break during which withdrawal bleeding will usually occur. The next pack should be commenced after seven tablet free days. The woman should be advised that her first cycle after taking all Norinyl-1 21 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. Norinyl-1 is effective from the first day if the tablets are taken as described above.

Changing From Another Pill

If a woman is switching to Norinyl-1 21 day from another 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 21 day pack on the eighth day by taking a white active tablet which corresponds to the day of the week. A non-hormonal contraceptive method (other than the rhythm or temperature method), should be used during the first Norinyl-1 21 day cycle until seven consecutive white active tablets have been taken.

If a woman is switching to Norinyl-1 21 day from a 28 day oral contraceptive pack, then all tablets in the current 28 day pack should be finished and Norinyl-1 21 day started on the next day by taking a white active tablet which corresponds to the day of the week. Once all 21 white active tablets have been taken, the woman should have seven tablet free days during which withdrawal bleeding will usually occur. The next pack should be commenced on the eighth day. During the first Norinyl-1 21 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 the changeover, a period of shortened duration or no period may occur.

28 DAY PACK

Norinyl-1 28 Day Pack

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.

DOSAGE AND ADMINISTRATION (Cont'd)

28 DAY PACK (Cont'd)

Norinyl-1 28 Day Pack (Cont'd)

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 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 with either Norinyl-1 21 or 28 day, the woman is instructed to continue the regimen since such bleeding is usually without significance. If the bleeding is persistent or prolonged, the woman is advised to consult her physician.

Norinyl-1 21 or 28 day can be prescribed postpartum for the nonlactating mother or postabortum as soon as the first normal menstrual period following a normal biphasic cycle occurs. If a further pregnancy is contraindicated for medical reasons, medication with Norinyl-1 21 or 28 day must be initiated by the 12th (but not before the 7th) day postpartum, or immediately postabortum or by the 5th day postabortum at the latest. When oral contraceptives are administered in the immediate postpartum/postabortum period, the increased risk of thromboembolic disease must be considered.

DOSAGE AND ADMINISTRATION (Cont'd)

Norinyl-1 21 and 28 Day Packs

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 (if using a 28 day pack) or the 7 tablet free days (if using a 21 day pack), she should start a new pack on the next day after having taken the last white active table from the green section of the current pack (i.e. skip the orange inactive tablets or the tablet free days). 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 21 or 28 day is resumed. In the case of the continuous intake of active tablets from two packs of Norinyl-1 21 or 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 21 or 28 day is resumed.

Concurrent Medication

If the woman is taking other drugs that may interact with norethisterone or mestranol from her 21 day or 28 day pack, then she should continue to take her tablets as usual but also employ a nonhormonal method of contraception (other than the rhythm or temperature method) during the time she is taking the interacting medication and continue for seven days after the medication is stopped. If these seven days extend into the inactive orange tablet section (if using a 28 day pack) or the 7 tablet free days (if using a 21 day pack), 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 or the tablet free days). 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 21 or 28 day. If, however, vomiting or diarrhoea occur during or shortly after the intake of Norinyl-1 21 or 28 day, contraceptive reliability may be jeopardised. Tablet taking should not be interrupted, to avoid premature withdrawal bleeding. A nonhormonal 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 (if using a 28 day pack) or the 7 tablet free days (if using a 21 day pack), 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 or the

DOSAGE AND ADMINISTRATION (Cont'd)

Norinyl-1 21 and 28 Day Packs (Cont'd)

tablet free days). 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 21 or 28 day is protracted, other methods of contraception should be considered.

Missed Period

See "WARNINGS AND PRECAUTIONS - NO. 25".

CONTRAINDICATIONS

As with all combined progestogen/oestrogen oral contraceptives, the following conditions should be regarded as contraindications:

1. Hypersensitivity to any component of the medicine.
2. Thrombophlebitis or thromboembolic disorders.
3. A past history of deep vein thrombophlebitis, or thromboembolic disorders.
4. Cerebrovascular or coronary artery disease or history of such disorders.
5. Known or suspected carcinoma of the breast.
6. Known or suspected carcinoma of genital organs.
7. Known or suspected oestrogen dependent neoplasia.
8. Undiagnosed abnormal vaginal bleeding.
9. Known or suspected pregnancy.
10. Liver disease including liver tumours or history of such tumours.
11. Hepatic dysfunction.
12. A history of jaundice, cholestatic jaundice or pruritus of pregnancy.
13. Dubin-Johnson or Rotor Syndrome.
14. Herpes gestationis, a condition of the pemphigoid group of bulbous skin diseases, not to be confused with Herpes simplex or genitalis.
15. A history of otosclerosis with deterioration during pregnancy.
16. Sickle-cell anaemia.
17. Abnormal lipid metabolism.
18. Hemiplegic migraine.

WARNINGS AND PRECAUTIONS

As with all combined progestogen/oestrogen oral contraceptives, the following conditions should be regarded as warnings and precautions:

1. The physician should be alert to the earliest manifestations of thrombotic disorders and medication should be discontinued immediately should any of these occur. Thromboembolic disorders and other vascular problems including cerebrovascular disorders and myocardial infarction may persist following termination of oral contraceptives. The risk of thrombotic and cardiac effects from oral contraceptives increases with age, especially for women over the age of 35 years, and is aggravated by cigarette smoking.
2. The risk of vascular disease is dose related.
3. Oral contraceptive medication should be discontinued at least six weeks prior to and 2 weeks after elective surgery because of the danger of thrombosis.
4. If there is a sudden, partial or complete loss of vision or if there is a sudden onset of proptosis, retinal thrombosis, or diplopia medication should be discontinued and examination made. If examination reveals papilloedema or retinal vascular lesions the medication should be discontinued.
5. The onset of or exacerbation of migraine or the development of headaches of a new pattern which are recurrent, persistent to severe, requires discontinuation of oral contraceptives and evaluation of the cause.
6. Diarrhoea or vomiting can jeopardise the contraceptive effect by affecting absorption.
7. Organic disease should be excluded when breakthrough bleeding appears for the first time in women who have been previously well controlled and in all cases of irregular vaginal bleeding.
8. Recovery of fertility may be delayed following use.
9. Before prescribing oral contraceptives physical examination is desirable including especially breasts, pelvis and liver. Annual physical examinations are also recommended.
10. Under the influence of oral contraceptives pre-existing uterine fibroids may increase in size.
11. Benign or malignant hepatic tumours have been associated with oral contraceptive use.
12. The use of oral contraceptives has also been associated with a possible increased incidence of gall bladder disease.
13. Acute renal failure, malignant hypertension, and haemolytic uraemic syndrome have been associated with the use of oral contraceptives.
14. Susceptible women may experience a rise in blood pressure during therapy.
15. Discontinue oral contraceptives during prolonged periods of bed rest.

WARNINGS AND PRECAUTIONS (Cont'd)

16. The use of oral contraceptives has been associated with an increased risk of breast cancer particularly at a young age. This increased relative risk appears to be related to duration of use.
17. The use of oral contraceptives may cause fluid retention. Patients with conditions such as diabetes, hypertension, epilepsy, migraine, asthma and cardiac or renal dysfunction require careful observation whilst on oral contraceptive therapy.
18. Patients with a history of emotional disorders, especially the depressive type are more prone to have a recurrence of depression while taking oral contraceptives. Medication should be discontinued if serious depression recurs.
19. Active ingredients of oral contraceptives have been detected in milk of mothers receiving these medicines and the effect on breast-fed infants is unknown. Suppression of lactation may occur.
20. Patients with diseases affecting calcium or phosphorus metabolism should be carefully observed.
21. Because oestrogens may hasten epiphyseal closure oral contraceptives should be used judiciously in young patients in whom bone growth is not complete.
22. Oral contraceptives may cause alterations in lipid metabolism.
23. A decrease in glucose tolerance occurs in a significant number of patients on oral contraceptives.
24. The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted (for further information see the section entitled "INTERACTIONS").
25. Since the safety of oral contraceptives in pregnancy has not been established it is recommended that for any patient who has missed a period pregnancy should be ruled out before continuing medication.
26. Some medicines accelerate the metabolism of oral contraceptives concurrently. Medicines suspected of having the capacity to reduce the efficiency of oral contraceptives are listed under the section entitled "INTERACTIONS". It is advisable to use non-hormonal methods of contraception during treatment with such medicines.

ADVERSE EFFECTS

The following adverse effects have been reported and are believed to be related to oral contraceptives:

Thrombophlebitis, arterial thromboembolism, pulmonary embolism, myocardial infarction, cerebral haemorrhage, cerebral thrombosis, mesenteric thrombosis, retinal thrombosis, hepatic adenomas, carcinomas or benign liver tumours, nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, breast changes (tenderness,

ADVERSE EFFECTS (Cont'd)

enlargement, secretion), spotting, changes in menstrual flow, amenorrhoea, temporary infertility after discontinuation of treatment, changes in cervical erosion and cervical secretions, amenorrhoea during and after treatment, anovulation post treatment, cholestatic jaundice, pruritus, allergic rash, photosensitivity, alopecia, chloasma, melasma which may persist, erythema multiforme, erythema nodosum, haemorrhagic eruption, hirsutism, headache, migraine, dizziness, drowsiness, changes in appetite, change in weight (increase or decrease), diminution in lactation when given immediately post-partum, mental depression, reduced tolerance to carbohydrates, vaginal candidiasis, changes in corneal curvature (steepening), intolerance to contact lenses, impaired renal function.

INTERACTIONS

Oral contraceptives may be rendered less effective by virtue of interaction with phenylbutazone, analgesics, antihistamines, antimigraine preparations, tranquillizers, anticonvulsants (barbiturates, primidone, phenytoin), and antibiotics (ampicillin, chloramphenicol, griseofulvin, isoniazid, neomycin, nitrofurantoin, penicillin V, rifampicin, sulfonamides and tetracyclines). Oral contraceptives may be also affected by the enzyme induction of St John's Wort (*Hypericum perforatum*). This may reduce the contraceptive efficacy.

Oral contraceptives may alter the effectiveness of other types of medicines, such as anticonvulsants, antihypertensive agents (for example, guanethidine), beta-blockers, hypnotics, hypoglycaemic agents, oral anticoagulants, theophylline, tranquillizers, tricyclic antidepressants and vitamins.

Oral contraceptives may cause alterations in certain laboratory estimations. A medicine free period of two months may be required before some of these parameters return to normal.

Laboratory Data

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

1. Increased norepinephrine-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 by radioimmunoassay. Free T₃ resin uptake is decreased reflecting the elevated TBG. Free T₄ concentration is unaltered.
3. Other binding proteins may be elevated in serum.
4. 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.
5. Triglycerides may be increased.
6. Glucose tolerance may be decreased.
7. Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

INTERACTIONS (Cont'd)

Laboratory Data (Cont'd)

8. Metyrapone test - decrease in urinary 17-ketosteroids and 17-ketogenic steroids.
9. Pregnanediol determinations - decrease in urinary pregnanediol levels.
10. False positive rheumatoid factors and antinuclear factor.
11. Lipid metabolism may be affected with increased serum levels of HDL cholesterol, triglycerides and phospholipids being observed.
12. Serum albumin levels are usually decreased (along with the associated calcium levels).

With the following tests abnormal results may indicate impairment of organ function:

1. Liver - increase in serum transaminases, alkaline phosphatase, gamma glutamyl transpeptidase, bilirubin, binding proteins and bromsulphalein retention.
2. Increased prothrombin and factors VII, VIII, IX and X; Decreased antithrombin III.

OVERDOSAGE

Symptoms

Overdosage may be manifested by nausea, vomiting, breast enlargement and vaginal bleeding.

Serious ill effects have not been reported following acute ingestions of large doses of oral contraceptives by young children.

Treatment

There is no specific antidote and treatment should be symptomatic. If a patient is seen within three hours of swallowing a significant number of tablets, emesis may be induced with syrup of ipecacuanha (15mL for a child one year and older, followed by a large glass of fluid; this may be repeated once only if vomiting does not occur).

PHARMACEUTICAL PRECAUTIONS

Store below 25°C.

MEDICINE CLASSIFICATION

Prescription medicine.

PACKAGE QUANTITIES

Norinyl-1 21 (21 day pack): 3 x 21

Norinyl-1 28 (28 day pack): 3 x 28

FURTHER INFORMATION

Nil.

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