NORIDAY*
Norethisterone

1. NAME OF THE MEDICINAL PRODUCT

Noriday 350 microgram tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 350 micrograms norethisterone.

Excipient(s) with known effect
Each tablet contains 62.25 mg lactose (as monohydrate)
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet
White, flat, circular, bevel-edged, tablet inscribed 'SEARLE' on one side and 'NY' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Contraception

4.2 Posology and Method of Administration

Posology

Starting on the first day of menstruation, one pill every day without a break in medication for as long as contraception is required. Additional contraceptive precautions (such as a condom) should be taken for the first 7 days of the first pack. Pills should be taken at the same time each day.

Missed pills

If a pill is missed within 3 hours of the correct dosage time then the missed pill should be taken as soon as possible; this will ensure that contraceptive protection is maintained. If a pill is taken 3 or more hours late it is recommended that the woman takes the last missed pill as soon as possible and then continues to take the rest of the pills in the normal manner. However, to provide continued contraceptive protection it is recommended that an alternative method of contraception, such as a condom, is used for the next 7 days.

Changing from another oral contraceptive

In order to ensure that contraception is maintained it is advised that the first pill is taken on the day immediately after the patient has finished the previous pack.

Use after childbirth, miscarriage or abortion

The first pill should be taken on the 21st day after childbirth. This will ensure the patient is protected immediately. If there is any delay in taking the first pill, contraception may not be established until 7 days after the first pill has been taken. In these circumstances women should be advised that extra contraceptive methods will be necessary.

After a miscarriage or abortion patients can take the first pill on the next day; in this way they will be protected immediately.

Vomiting and diarrhoea

Gastrointestinal upsets, such as vomiting and diarrhoea, may interfere with the absorption of the pill leading to a reduction in contraceptive efficacy. Women should continue to take Norethisterone, but they should also be advised to use another contraceptive method during the period of gastrointestinal upset and for the next 7 days.

Method of administration

For oral use.

4.3 Contraindications

The contraindications for progestogen-only oral contraceptives are:

(i) known, suspected, or a past history of breast, genital or hormone dependent cancer
(ii) acute or severe chronic liver diseases including past or present liver tumours, Dubin-Johnson or Rotor syndrome
(iii) active liver disease
(iv) history during pregnancy of idiopathic jaundice or severe pruritus
(v) disorders of lipid metabolism
(vi) undiagnosed abnormal vaginal bleeding
(vii) known or suspected pregnancy
(viii) hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Combined oestrogen/progestogen preparations have been associated with an increase in the risk of thromboembolic and thrombotic disease. Risk has been reported to be related to both oestrogenic and progestogenic activity. In the absence of long-term epidemiological studies with progestogen-only oral contraceptives, it is required that the existence, or history of thrombophlebitis, thromboembolic disorders, cerebral vascular disease, myocardial infarction, angina, or coronary artery disease be described as a contraindication to Norethisterone as it is to oestrogen containing oral contraceptives.

4.4 Special Warnings and Precautions for Use

Assessment of women prior to starting oral contraceptives (and at regular intervals thereafter) should include a personal and family medical history of each woman. Physical examination should be guided by this and by the contraindications (section 4.3) and warnings (section 4.4) for this product. The frequency and nature of these assessments should be based upon relevant guidelines and should be adapted to the individual woman, but should include measurement of blood pressure and, if judged appropriate by the clinician, breast, abdominal and pelvic examination including cervical cytology.

Malignant hepatic tumours have been reported on rare occasions in long-term users of contraceptives. Benign hepatic tumours have also been associated with oral contraceptive usage. A hepatic tumour should be considered in the differential diagnosis when upper abdominal pain, enlarged liver or signs of intra-abdominal haemorrhage occur.

Hepatic adenoma - In very rare cases, hepatic adenomas may be associated with progesterone-only pill (POP) use. In some cases, the hepatic adenoma may decrease in size or become undetectable after discontinuation of Norethisterone. Rupture of hepatic adenomas may cause death through intra-abdominal haemorrhage. In extremely rare cases, hepatocellular carcinoma may be associated with combined oral contraceptives use.

A statistical association between the use of oral contraceptives and the occurrence of thrombosis, embolism or haemorrhage has been reported. Patients receiving oral contraceptives should be kept under regular surveillance, in view of the possibility of development of conditions such as thrombo-embolism.

The risk of coronary artery disease in women taking oral contraceptives is increased by the presence of other predisposing factors such as cigarette smoking, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxaemia and increasing age. After the age of thirty-five years, the patient and physician should carefully re-assess the risk/benefit ratio of using oral contraceptives as opposed to alternative methods of contraception.

Norethisterone should be discontinued at least 4 weeks before elective surgery or during periods of prolonged immobilisation. It would be reasonable to resume Norethisterone 2 weeks after surgery provided the woman is ambulant. However, every woman should be considered individually with regard to the nature of the operation, the extent of immobilisation, the presence of additional risk factors and the chance of unwanted conception.

Norethisterone should be discontinued if there is a gradual or sudden, partial or complete loss of vision or any evidence of ocular changes, onset or aggravation of migraine or development of headache of a new kind which is recurrent, persistent or severe, suspicion of thrombosis or infarction, significant rise in blood pressure or if jaundice occurs.

Caution should be exercised where there is the possibility of an interaction between a pre-existing disorder and a known or suspected side effect. The use of Norethisterone in women suffering from epilepsy, or with a history of migraine or cardiac or renal dysfunction may result in exacerbation of these disorders because of fluid retention. Caution should also be observed in women who wear contact lenses, women with impaired carbohydrate tolerance, depression, gallstones, a past history of liver disease, varicose veins, hypertension, asthma or any disease that is prone to worsen during pregnancy (e.g. multiple sclerosis, porphyria, tetany and otosclerosis).

Progestogen-only oral contraceptives may offer less protection against ectopic pregnancy, than against intrauterine pregnancy.

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk of having breast cancer diagnosed in women who are currently using oral contraceptives (OC). The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in OC users, the biological effects of OCs or a combination of both. The additional breast cancers diagnosed in current users of OCs or in women who have used OCs in the last ten years are more likely to be localised to the breast than those in women who never used OCs.

Breast cancer is rare among women under 40 years of age whether or not they take OCs. Whilst the background risk increases with age, the excess number of breast cancer diagnoses in current and recent progesterone-only pill (POP) users is small in relation to the overall risk of breast cancer, possibly of similar magnitude to that associated with combined OCs. However, for POPs, the evidence is based on much smaller populations of users and so is less conclusive than that for combined OCs.

The most important risk factor for breast cancer in POP users is the age women discontinue the POP; the older the age at stopping, the more breast cancers are diagnosed. Duration of use is less important and the excess risk gradually disappears during the course of the 10 years after stopping POP use, such that by 10 years there appears to be no excess.

The evidence suggests that compared with never-users, among 10,000 women who use POPs for up to 5 years but stop by age 20, there would be much less than 1 extra case of breast cancer diagnosed up to 10 years afterwards. For those stopping by age 30 after 5 years use of the POP, there would be an estimated 2-3 extra cases (additional to the 44 cases of breast cancer per 10,000 women in this age group never exposed to oral contraceptives). For those stopping by age 40 after 5 years use, there would be an estimated 10 extra cases diagnosed up to 10 years afterwards (additional to the 160 cases of breast cancer per 10,000 never-exposed women in this age group).

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

Norethisterone contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

The herbal remedy St. John's Wort (*Hypericum perforatum*) should not be taken concomitantly with this medicine as this could potentially lead to a loss of contraceptive effect.

Some drugs may modify the metabolism of Norethisterone reducing its effectiveness; these include certain sedatives, antibiotics, and antiepileptics. During the time such agents are used concurrently, it is advised that an alternative method of contraception, such as a condom, is also used.

The serum levels of prednisone, prednisolone, cloprednol and possibly other corticosteroids are considerably increased in those taking oral contraceptives. Both the therapeutic and toxic effects may be expected to increase accordingly.

4.6 Fertility, Pregnancy and Lactation

Pregnancy

Noriday is not indicated during pregnancy. If pregnancy occurs during medication with Noriday, treatment should be withdrawn immediately. Like all norethisterone derivatives used

for contraception, Noriday has slight androgenic activity. At doses higher than normally used in OC and HRT formulations, masculinisation of female foetuses has been observed. The results of most epidemiological studies to date relevant to inadvertent foetal exposure to combinations of oestrogens with progestogens, indicate no teratogenic or foetotoxic effects.

Breast-feeding
There is no evidence that Norethisterone tablets diminish the yield of breast milk. Small amounts of steroid materials appear in the milk; their effect on the breast-fed child has not been determined.

4.7 Effects on Ability to Drive and Use Machines

Not relevant.

4.8 Undesirable Effects

The incidence of side effects in clinical trials was lower than that experienced with oestrogen-containing oral contraceptives. Side effects which did occur included some cycle irregularity during the first few months of therapy, spotting or breakthrough bleeding, amenorrhoea, breast discomfort, gastrointestinal symptoms, rash, headaches, migraine, depression, fatigue, nervousness, disturbance of appetite and changes in weight, hepatic adenoma and libido.

Hypertension, which is usually reversible on discontinuing treatment, has occurred in a small percentage of women taking oral contraceptives.

Menstrual pattern: Women taking Norethisterone for the first time should be informed that they may initially experience menstrual irregularity. This may include amenorrhoea, prolonged bleeding and/or spotting but such irregularity tends to decrease with time. If a woman misses two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen.

4.9 Overdose

Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may be manifested by nausea, vomiting, breast enlargement and vaginal bleeding. There is no specific antidote and treatment should be symptomatic. Gastric lavage may be employed if the overdose is large and the patient is seen sufficiently early (within four hours).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: sex hormones and modulators of the genital system, progestogens, ATC code: G03DC02.

Norethisterone administration increases the protein and sialic acid content of cervical mucus which prevents penetration of the mucus by spermatozoa. It causes changes in the structure of the endometrium such that implantation of blastocysts is impaired. It also reduces numbers and height of cilia on cells lining the fallopian tube, which could delay tubal transport of ova.

5.2 Pharmacokinetic Properties

Norethisterone is rapidly and completely absorbed after oral administration, peak plasma concentrations occurring in the majority of subjects between 1 and 3 hours. Due to first-pass metabolism, blood levels after oral administration are 60% of those after i.v. administration. The half-life of elimination varies from 5 to 12 hours, with a mean of 7.6 hours. Norethisterone is metabolised mainly in the liver. Approximately 60% of the administered dose is excreted as metabolites in urine and faeces.

5.3 Preclinical Safety Data

The toxicity of norethisterone is very low. Reports of teratogenic effects in animals are uncommon. No carcinogenic effects have been found even in long-term studies. In subacute and chronic studies only minimal differences between treated and control animals are observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Maize starch
Polyvidone
Magnesium stearate
Lactose monohydrate

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

The shelf life of Norethisterone tablets is 5 years.

6.4 Special Precautions for Storage

Store below 30°C.

Store in a cool, dry place away from direct sunlight.

6.5 Nature and Contents of Container

PVC blisters/foil backing in a cardboard carton. Each strip has 4 rows of 7 tablets. Each carton contains 3 x 28 tablets.

6.6 Special Instructions for Use/Handling

No special requirements.

7. MANUFACTURER

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