AUSTRALIAN PRODUCT INFORMATION – NORIDAY® 28-DAY (NORETHISTERONE) TABLETS

1. NAME OF THE MEDICINE

Norethisterone

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each NORIDAY tablet contains 0.35 mg norethisterone.

Excipients with known effect

Lactose monohydrate

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Tablets.

NORIDAY Tablets are available as round white tablets marked "SEARLE" on one side and "NY" on the reverse in "calendar" packs of 28 tablets in PVC/aluminium blister.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NORIDAY is an oral contraceptive for women who will not, or cannot tolerate other oral contraceptives or intrauterine devices.

Advice to the Patient

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

4.2 Dose and method of administration

One NORIDAY 0.35 mg tablet should be taken daily, at about the same time each day starting on the first day of menstruation. Tablets should be taken continuously, without interruption, whether bleeding occurs or not. This is especially important for patients new to progestogen-only oral contraception. Each subsequent pack is started on the day after the previous pack is finished.

If a tablet is missed and there is a delay of more than 3 hours after the normal time of taking the tablet, protection is reduced and additional means of contraception should be used along

with NORIDAY until menstrual bleeding occurs. The patient should be advised that if prolonged bleeding occurs, she should consult her physician.

If the patient has missed 1 or 2 tablets and does not have a period within 6 weeks of the last period, she should stop taking NORIDAY and use another method of nonhormonal contraception until pregnancy has been ruled out. If more than 2 tablets have been missed, NORIDAY should be discontinued immediately and a method of nonhormonal contraception should be used until menses has occurred or pregnancy has been excluded. Alternatively, if the patient has taken the tablets correctly, and if menses does not appear within 60 days from the last period, a method of nonhormonal contraception should be substituted until pregnancy is ruled out. The possibility of pregnancy should be considered before tablet-taking is resumed if three or more tablets have been missed.

NORIDAY may be prescribed in the postpartum period either immediately or at the first postpartum examination whether or not menstruation has resumed.

4.3 Contraindications

- Thrombophlebitis, thromboembolic disorders, cerebral vascular disease, myocardial infarction, or a history of these conditions.
- Patients with liver disease or history of cholestatic jaundice of pregnancy and in Dubin-Johnson Syndrome or Rotor Syndrome.
- Hepatic adenomas or carcinomas.
- Known or suspected carcinoma of the breast and/or genital organs, or known or suspected hormone-dependent neoplasia.
- Undiagnosed abnormal genital bleeding.
- Known or suspected pregnancy.
- Sickle cell anaemia.
- Disturbed lipid metabolism.
- History of herpes of pregnancy.
- Otosclerosis with deterioration in previous pregnancy.
- Hypersensitivity to any component of the product.

4.4 Special warnings and precautions for use

The effects of long-term use with low dose single progestogen therapy remain to be determined. Until then, the same precautions (outlined below) associated with oestrogen-progestogen combination therapy should apply to progestogen-only contraceptives.

General

Before prescribing oral contraceptives, a complete medical family history and physical examination is desirable. The pre-treatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Papanicolaou smear and laboratory tests. Such medical examinations should be repeated periodically during the use of progestogen-only contraceptives.

The effectiveness of progestogen only oral contraceptives, such as NORIDAY, is lower than that of the sequential or combination oral contraceptives containing both oestrogen and progestogen. If 100 women utilised an oestrogen containing oral contraceptive for a period of 1 year, generally less than 1 pregnancy would be expected to occur; however, if NORIDAY had been utilised approximately 4 pregnancies might occur.

An alteration in menstrual patterns in many patients is likely to be induced by using continuous progestogens. The amount and duration of flow, and cycle length, will probably be quite variable; therefore, the physician should be alert to the possibility of other causes of irregular genital bleeding and consider adequate diagnostic measures. The patient should be advised that if prolonged bleeding occurs she should consult her physician. If one menstrual period is missed and the progestogen-only contraceptive has not been taken according to directions, or if two consecutive menstrual periods are missed, the possibility of pregnancy should be evaluated. In addition, a non-hormonal backup method of contraception should be used

The efficacy of NORIDAY may be affected when absorption is impaired by vomiting or diarrhoea. If in doubt about the absorption of a tablet, the patient should be advised to treat the incident as a missed tablet (see section 4.2 Dose and method of administration).

Thromboembolic Disorders

An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. The physician should be alert to the earliest manifestations of thrombotic and thromboembolic disorders, e.g., thrombophlebitis, cerebrovascular disorders (including haemorrhage), myocardial infarction, pulmonary embolism, mesenteric thrombosis and retinal thrombosis. Should any of these occur or be suspected, the drug should be discontinued immediately.

A two to six fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of oral contraceptives, therefore, the physician should consider discontinuing therapy at least six weeks prior to and two weeks after elective surgery. It is also recommended that oral contraceptive therapy should be discontinued during prolonged periods of bed rest.

Care should be used when prescribing progestogen-only contraceptives to women predisposed to thromboembolic disorders (e.g., a history of thromboembolic events, thrombophilia, cardiovascular disease or women who are obese or experience prolonged immobilisation).

Myocardial Infarction

An increased risk of myocardial infarction and transient ischaemic attack associated with the use of oral contraceptives has been reported confirming a previously suspected association. Studies found that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolaemia, obesity, diabetes, history of pre-eclamptic toxaemia) the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not. Oral contraceptives, however, were found to be an additional factor. As the risk of .myocardial infarction is substantially increased in women aged 40 or over, the use of oral contraceptives in women of this age group is not recommended.

In terms of relative risk, it has been estimated that oral contraceptive users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as non-users who smoke.

Cigarette Smoking

Cigarette smoking increased the risk of serious adverse effects on the heart and blood vessels from oral contraceptive use. The risk increases with age particularly after 30 years and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should not smoke.

Elevated Blood Pressure

Susceptible women may experience a rise in blood pressure following the administration of contraceptive steroids. Blood pressure should be measured at intervals and care should be exercised in prescribing these preparations for patients with hypertension.

Ocular Lesions

There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis with the use of oral contraceptives. Oral contraceptives should be discontinued if there is gradual or sudden, partial or complete loss of vision; onset of proptosis or diplopia; onset or aggravation of migraine or development of headache of a new pattern which is recurrent, persistent or severe; papilloedema; or any evidence of retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be taken immediately.

Hepatic Tumours

Benign hepatic adenomas appear to be associated with the use of oral contraceptives. Although benign and rare, hepatic adenomas may rupture and cause death through intra-abdominal bleeding. This has been reported in short-term as well as long-term users of oral contraceptives, although one study relates risk with duration of use of the contraceptive. While hepatic adenoma is a rare lesion, it should be considered in women presenting with abdominal pain and tenderness, abdominal mass or shock.

A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives. The relationship of these drugs to this type of malignancy is not known at this time.

Carcinoma of Breast

Although there is no confirmed evidence to indicate that an increased risk of cancer is associated with the use of oral contraceptives, close clinical surveillance is nevertheless essential in all women taking these drugs.

Studies reported a slightly increased relative risk of having breast cancer diagnosed in women who are currently using combined oral contraceptives (COC) and progestin only contraceptives compared to never-users. The increased risk gradually disappears during the course of the 10 years after cessation of COC use. These studies do not provide evidence for causation. The observed pattern of increased risk of breast cancer diagnosis may be due to earlier detection of breast cancer in COC users (due to more regular clinical monitoring), the biological effects of COCs, or a combination of both. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the lifetime risk of breast cancer. Breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users. The risk of having breast cancer diagnosed in progestogen-only pill users is possibly of similar magnitude to that associated with COC. However, for progestogen-only preparations, the evidence is based on much smaller populations of users and so is less conclusive than that for COCs.

Carcinoma of reproductive organs

In cases of undiagnosed, persistent, or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to eliminate the possibility of malignancy. Women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care.

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.

Ectopic Pregnancy

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

In addition, the symptoms of ectopic pregnancy and the adverse reactions to low dose progestogen administration (i.e. breakthrough bleeding, spotting, menstrual irregularity and

amenorrhoea) are similar. The possibility of an ectopic pregnancy should be considered whenever a patient receiving a low-dose progestogen contraceptive experiences pelvic discomfort.

Delayed Follicular Atresia (Ovarian Cysts)

If follicular development occurs, atresia of the follicle is sometimes delayed and the follicle may continue to grow beyond the size it would attain in a normal cycle. Generally, these enlarged follicles are asymptomatic, in some cases they may be associated with mild abdominal pain.

Carbohydrate and Lipid Effects

A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. For this reason, prediabetics and diabetics should be carefully observed while receiving oral contraceptives.

An increase in triglycerides and total phospholipids has been observed in patients receiving oral contraceptives.

Liver Disease

Women with a history of oral contraceptive related cholestasis or women with cholestasis during pregnancy are more likely to have this condition with oral contraceptive use. If these patients receive progestogen-only oral contraceptives they should be carefully monitored and, if the condition recurs, progestogen-only oral contraceptive use should be discontinued.

Progestins may be poorly metabolised in patients with impaired liver function. If progestogen-only oral contraceptives are prescribed for these patients, they should be carefully observed.

Migraine/Headache

The onset or exacerbation of migraine or development of headache with a new pattern that is recurrent, persistent, or severe requires discontinuation of progestogen-only oral contraceptives and evaluation of the cause.

Women with migraine (particularly migraine with aura) who take progestogen-only oral contraceptives may be at increased risk of stroke.

Fluid Retention

Progestogens may cause some degree of fluid retention. Conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.

Depressive Disorder

Oral contraceptives may cause depressive disorder. Patients with a history of depressive disorder should be carefully observed during treatment.

Prolonged Therapy

Any possible influence of prolonged NORIDAY therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. The age of the patient constitutes no absolute limiting factor, although treatment with NORIDAY may mask the onset of the climacteric.

Use in the elderly

No data available.

Paediatric use

Use of this product before menarche is not indicated.

Effects on laboratory tests

The pathologist should be advised of NORIDAY therapy when relevant specimens are submitted.

4.5 Interactions with other medicines and other forms of interactions

The effectiveness of progestin-only pills may be reduced by hepatic enzyme-inducing drugs such as phenytoin, primidone, carbamazapine, barbiturates, rifampicin and other antibiotics such as ampicillin and griseofulvin, some protease inhibitors, and possibly St. John's wort. During concomitant use of progestogen-only oral contraceptives and substances that may affect the contraceptive efficacy of progestogen-only oral contraceptives, it is recommended that a non-hormonal back-up method of birth control be used in addition to the regular intake of NORIDAY. Use of a non-hormonal back-up method of birth control is advisable after discontinuation of substances that have led to induction of hepatic microsomal enzymes. It may take several weeks until enzyme induction has subsided, depending on dosage, duration of use, and rate of elimination of the inducing substance. For women receiving long-term therapy with hepatic enzyme inducers, another method of contraception should be considered.

Other mechanisms which may affect the contraceptive efficacy of progestogen-only oral contraceptives include any substance that reduces gastrointestinal transit time.

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

NORIDAY should be administered at least 2 hours apart from antacids, as antacids may impair the absorption of NORIDAY.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No data available.

Use in pregnancy – Pregnancy Category [B3]

Animal studies have shown that high doses of progestogens can cause masculinization of the female foetus.

Use in lactation

Numerous studies have evaluated progestogen-only oral contraceptive use in breast-feeding women and their infants. Small amounts of progestins and/or their metabolites have been identified in the milk of nursing mothers. Very rarely, adverse effects on the child have been reported, including jaundice.

4.7 Effects 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)

Adverse Reaction by System Organ Class

Reproductive system and breast disorders

Amenorrhea, breakthrough bleeding/spotting, menstrual irregularities, breast pain, enlargement, tenderness, secretion; galactorrhea; ectopic pregnancy; delayed follicular atresia; vaginal discharge; vaginitis, masculinisation of the female foetus, change in cervical erosion.

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Hepatic adenoma.

Metabolism and nutrition disorders

Glucose intolerance, changes in appetite (increase or decrease), exacerbation of porphyria.

Psychiatric disorders

Mood Disturbances, mental depression, decreased libido.

Nervous system disorders

Headache, including severe headache, dizziness, nervousness.

Eye disorders

Retinal vascular thrombosis.

Vascular disorders

Pulmonary embolism, venous thromboembolism; including deep vein thrombosis and thrombophlebitis, myocardial infarction, stroke.

Gastrointestinal disorders

Abdominal pain, abdominal cramps, abdominal distention, nausea, vomiting, gastrointestinal disturbance.

Hepato-biliary disorders

Cholestasis, cholestatic jaundice.

Skin and subcutaneous tissue disorders

Acne, alopecia, hirsutism, chloasma/melasma that may persist, rash (allergic) with or without pruritus.

Musculoskeletal, connective tissue and bone disorders

Leg cramp, pain.

Immune system disorders

Anaphylactic/anaphylactoid reactions including urticaria, throat tightness, facial edema.

General disorders and administration site reactions

Fatigue, oedema.

Investigations

Increased AST, ALT, bilirubin, decreased HDL, increased blood pressure, changes in weight (increase or decrease).

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

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, fatigue, somnolence and withdrawal bleeding may occur in females.

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

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

Norethisterone is a synthetic steroidal progestogen oral contraceptive. The mechanism of conception control is not known. Suggested mechanisms of action are increased viscosity of the cervical mucus, changes in the endometrium making it unsuitable for nidation to take place, some inhibition of the secretion of pituitary gonadotrophins.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

No data available.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate

Povidone

Maize starch

Lactose monohydrate.

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

NORIDAY Tablets are presented in "calendar" packs of 28 tablets in PVC/aluminium blister.

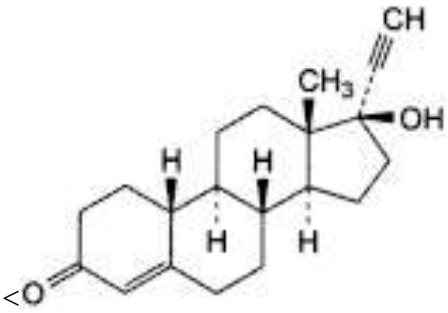
6.6 Special precautions for disposal

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

6.7 Physicochemical properties

Chemical structure

The chemical name of norethisterone is 17-hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one. The chemical structure of norethisterone is shown below. The empirical formula is $C_{20}H_{26}O_2$ and the molecular weight is 298.4.



Norethisterone (B.P.) is a white to creamy-white odourless crystalline powder with a slightly bitter taste, insoluble in water and sensitive to light.

CAS number

68-22-4

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription only medicine)

8. SPONSOR

Pfizer Australia Pty Ltd
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9. DATE OF FIRST APPROVAL

9 March 1993

10. DATE OF REVISION

18 February 2020

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Summary Table of Changes

Section changed	Summary of new information
All	PI reformatted to required TGA format
8	Update to Sponsor details