

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

NORETHINDRONE TABLETS, USP 0.35 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.35 mg of norethisterone.

Excipients with known effect

- Lactose anhydrous

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet

Light yellow to yellow round, flat faced beveled edged, uncoated tablets with '305' debossed on one side and a 'G' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For oral contraception in women for whom estrogens may not be appropriate.

4.2 Dose and method of administration

To achieve maximum contraceptive effectiveness, NORETHINDRONE TABLETS, USP must be taken exactly as directed. One tablet is taken every day at the same time, with no interruption, whether bleeding occurs or not. Each subsequent pack is started on the day after the previous pack is finished.

Contraceptive efficacy may be reduced if a tablet is taken more than 3 hours late.

To provide added protection during the first cycle only, the patient should be instructed to use an additional method of contraception (with the exception of rhythm, temperature and cervical- mucus methods).

How to start NORETHINDRONE TABLETS, USP

No preceding hormonal contraceptive use (in the past month)

Tablet-taking should start on the FIRST DAY of menstrual bleeding. If starting on another day, a non-hormonal back-up method of birth control (such as condoms and spermicide) should be used for the first 48 hours. Thereafter, one tablet is taken continuously at the same time every day preferably in the early evening even during menstrual bleeding.

Changing from another type of progestin-only method (implant, injection)

Tablet-taking should start on the day of an implant removal or, if using an injection, the day the next injection would be due. In addition, a non-hormonal back-up method of birth control should be used for the first 48 hours.

Changing from a combination oral contraceptive (COC)

Tablet-taking should start on the day after the last active tablet of the COC. Any inactive tablets from the COC package should not be taken.

Following miscarriage, abortion, or for postpartum women who are not breast-feeding

Tablet-taking may start immediately. In addition, a non-hormonal back-up method of birth control should be used for the first 48 hours.

Postpartum women who are breast-feeding

In women who are breast-feeding, tablet-taking may start six weeks after delivery. If needed, it may be started as early as Day 7. In addition, a non-hormonal back-up method of birth control should be used for the first 48 hours.

Management of missed tablets

Tablets must be taken at the same time each day in order to maintain adequate hormone levels.

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

If one tablet is missed and there is a delay of more than 3 hours after the normal time of taking it, it should be taken as soon as possible, with the next tablet being taken at the usual time even if it means taking two tablets on the same day. An additional method of non-hormonal contraception (with the exception of rhythm, temperature and cervical-mucus methods) should be used along with NORETHINDRONE TABLETS, USP for the next 48 hours, irrespective of bleeding.

If three or more tablets are missed, NORETHINDRONE TABLETS, USP should be discontinued immediately and a method of non-hormonal contraception should be used until menses has appeared or pregnancy has been excluded.

Note: This type of contraception is a little less reliable than the conventional “pill” and it is important to ensure that instructions with regard to administration are followed most carefully.

Advice in case of vomiting

Vomiting or diarrhoea may reduce the effectiveness of the tablets by preventing them from being fully absorbed. In the case of repeated vomiting or continued diarrhoea, additional non-hormonal contraceptive measures should be employed for the remainder of that course.

4.3 Contraindications

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

- Current thromboembolic process.
- Cerebral vascular or coronary artery disease or history of such disorders.
- Known or suspected carcinoma of the breast or genital organs or a history of such cancers.
- Undiagnosed abnormal vaginal bleeding.
- Known or suspected pregnancy.
- Acute or severe chronic liver disease.
- Hepatic adenomas or carcinomas, or a history of such tumours.
- A history during pregnancy of idiopathic jaundice or cholestatic jaundice.
- A history during pregnancy of severe pruritus.
- Dubin-Johnson or Rotor syndrome.
- Disturbances of lipometabolism or severe arterial disease.
- A history of ectopic pregnancy.
- Hypersensitivity to any component of the product.

4.4 Special warnings and precautions for use

Oral contraception should be stopped immediately following first signs of thrombophlebitis or thromboembolism, jaundice or pregnancy.

Malabsorption syndrome

Patients with malabsorption syndrome require careful observation whilst on progestogen contraceptives.

Thrombosis and thromboembolism

Increased risks of thrombotic and thromboembolic events, including cerebrovascular events, myocardial infarction, and transient ischemic attack have been associated with the use of

COCs. The available literature, which is limited because of infrequent use of POPs, does not suggest an increased risk of these conditions. However, there have been reports of these conditions coincident with the use of POPs. Therefore, the possibility of thrombosis should be considered.

Care should be used when prescribing POPs to women predisposed to thromboembolic disorders (e.g. a history of thromboembolic events, thrombophilia, cardiovascular disease; 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 toxemia) 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. 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.

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.

Elevated blood pressure

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

associated with oral contraceptive use. Blood pressure should be measured at intervals and care should be exercised in prescribing these preparations for patients with hypertension.

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.

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 a POP they should be carefully monitored and, if the condition recurs, POP use should be discontinued.

Progestins may be poorly metabolised in patients with impaired liver function. If POPs are prescribed for these patients, they should be carefully observed.

Hepatic adenoma

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

The relationship between occurrence of liver tumours and use of female sex hormones is not known at present. If the patient presents with a mass or tenderness in the right upper quadrant or an acute abdomen, the possible presence of a tumour should be considered.

Vomiting and diarrhoea

Vomiting or diarrhoea may reduce the effectiveness of the tablets by increasing gastrointestinal motility and reducing hormone absorption. In the case of repeated vomiting or continued diarrhoea, additional non-hormonal contraceptive measures should be employed for the remainder of that course (see section 4.2).

Carbohydrate effects

A decrease in glucose tolerance has been observed in a significant percentage of patients on estrogen-progestogen therapy. The mechanism of this decrease is obscure. For this reason diabetic patients as well as all other patients on NORETHINDRONE TABLETS, USP therapy should be carefully observed for any of the previously mentioned occurrences. Although some studies have shown that diabetic women taking POPs do not generally experience changes in insulin requirements, the possibility of potential clinical effects should be considered.

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.

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 POPs and evaluation of the cause.

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

Depressive disorder

Patients with a history of depression should be carefully observed and the medication discontinued if serious depression recurs.

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.

Ectopic pregnancy

Progestogen-only oral contraceptives such as NORETHINDRONE TABLETS, USP may offer less protection against ectopic pregnancy than against intra-uterine pregnancy. Health care providers should be alert to the possibility of an ectopic pregnancy in women who become pregnant or complain of lower abdominal pain while on progesterone-only oral contraceptives (POPs). Of the pregnancies reported in clinical studies of POP users, up to 10% are extra-uterine.

Genital bleeding

Irregular or intermenstrual bleeding may occur in women using POPs. A usual feature of all POPs is that they produce an initial irregularity of the bleeding pattern, but such irregularity tends to decrease with time. The patient should be informed before starting NORETHINDRONE TABLETS, USP tablets that her menstrual pattern is likely to alter. Irregular bleeding is, from a medical point of view, no reason for discontinuation of therapy, as long as organic causes and pregnancy can be ruled out. However, if such bleeding is suggestive of infection, malignancy, pregnancy or other conditions, such causes should be evaluated.

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

Missed withdrawal bleeding

If the patient does not adhere to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period and further use of oral contraceptives should be withheld until pregnancy has been ruled out. In addition, a non-hormonal back-up method of contraception should be used. It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If pregnancy is confirmed the patient should be apprised of the potential risks to the fetus and the advisability of continuing the pregnancy should be discussed in the light of these risks.

Prolonged therapy

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

Medical examinations

A complete personal and family history and physical examination should be taken prior to the initiation of POP use. Such medical examinations should be repeated periodically during the use of POPs.

Other

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

Acute renal failure, gallbladder disease and haemolytic uraemic syndrome and alterations in lipid metabolism have been associated with the use of oral contraceptives.

Visual disturbances have been associated with oral contraceptive use.

Pre-existing uterine fibroids may increase in size.

The pathologist should be advised of NORETHINDRONE TABLETS, USP therapy when relevant specimens are submitted. For further information see section 4.4 – Effects on laboratory tests.

Paediatric use

Use of this product before menarche is not indicated.

Effects on laboratory tests

Progestogen contraceptives may cause alterations in certain laboratory estimations. These parameters may take two months to return to normal following discontinuation of oral contraceptive therapy.

With the following tests abnormal results may reflect a biological interference with the test itself and not an impairment of organ function:

- Increase in serum amino-acid levels
- Decrease in pregnanediol excretion.

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

- Liver - increase in bilirubin, alkaline phosphatase and gamma glutamyl transpeptidase.

4.5 Interaction with other medicines and other forms of interaction

The interactions listed in this section have been associated with the use of oral contraceptives containing estrogen and progestogen:

The effectiveness of progestin-only pills may be reduced by hepatic enzyme-inducing drugs such as phenytoin, primidone, carbamazepine, barbiturates, rifampicin, other antibiotics (such as ampicillin, griseofulvin, sulphonamides, isoniazid, nitrofurantoin, tetracycline, penicillin V, neomycin and chloramphenicol), some protease inhibitors, analgesics, antihistamines, antimigraine preparations, tranquillizers and possibly St. John's wort. During concomitant use of POPs and substances that may affect the contraceptive efficacy of POPs, it is recommended that a non-hormonal back-up method of birth control be used in addition to the regular intake of NORETHINDRONE TABLETS, USP. 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 POPs include any substance that reduces gastrointestinal transit time.

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.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

It is advisable to discontinue the use of oral contraceptives three months before a planned pregnancy.

Extensive epidemiological studies have revealed no increased risk of birth defects in children born to women who used oral contraceptives prior to pregnancy.

Studies also do not suggest a teratogenic effect, particularly insofar as cardiac anomalies and limb-reduction defects are concerned, when taken inadvertently during early pregnancy (see section 4.3).

Breast-feeding

Numerous studies have evaluated POP 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.

Fertility

The limited available data do not indicate a significant delay in the return of the woman's normal ovulation and fertility following discontinuation of POPs.

4.7 Effects on ability to drive and use machines

None stated.

4.8 Undesirable effects

See section 4.4 for discussion of ectopic pregnancy, delayed follicular atresia (ovarian cysts), carcinoma of the reproductive organs and hepatic adenoma.

The following adverse effects have been observed in women taking progestogens:

System Organ Class

Adverse Reaction

Reproductive system and breast disorders

Amenorrhea, breakthrough
bleeding/spotting, menstrual irregularities,

breast changes (pain, enlargement, tenderness, secretion), galactorrhea, ectopic pregnancy, delayed follicular atresia, vaginal discharge, vaginitis, masculinisation of the female fetus, change in cervical erosion and cervical secretions.

Neoplasms benign, malignant and unspecified (inc. cysts and polyps)

Hepatic adenoma.

Metabolism and nutrition disorders

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

Psychiatric disorders

Mood disturbances (including 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 distension, nausea, vomiting,
gastrointestinal disturbance.

Hepatobiliary disorders

Cholestasi, 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
oedema.

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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions

<https://pophealth.my.site.com/carmreportnz/s/>

4.9 Overdose

Signs and symptoms

Overdose may be manifested by nausea, vomiting, breast tenderness, breast enlargement, dizziness, fatigue, somnolence and withdrawal bleeding in females.

Treatment of overdose

There is no specific antidote and treatment should be symptomatic.

{For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).}

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

NORETHINDRONE TABLETS, USP is a progestogen-only oral contraceptive. Although the mode of action of NORETHINDRONE TABLETS, USP has not yet been fully defined it is thought that alterations occur in the cervical mucus which inhibit the penetration of sperm, there is substantial inhibition of ovulation, and changes occur in the endometrium which inhibit implantation of the fertilised egg.

When taken consistently and correctly, the probable failure rate of POPs is 0.5% per year; however, the failure rate during typical use is 5% per year for all types of oral contraceptives. The efficacy of most methods of contraception depends upon the reliability with which they are used. Method failure is more likely if POP tablets are taken late or missed.

5.2 Pharmacokinetic properties

Absorption

Norethisterone is rapidly and completely absorbed after oral administration, peak plasma concentrations occurring in the majority of subjects between 1 and 3 hours.

Biometabolism

Due to first-pass metabolism, blood levels after oral administration are 60% of those after i.v. administration.

Elimination

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

Silicon dioxide

Corn starch

D&C Yellow No. 10

Ethylcellulose, unspecified

Anhydrous lactose

Magnesium stearate

Microcrystalline cellulose

Povidone, unspecified

Talc

6.2 Incompatibilities

None stated.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at 20°C to 25°C.

6.5 Nature and contents of container

NORETHINDRONE TABLETS, USP Carton of 3 dispensers each containing 28 tablets.

6.6 Special precautions for disposal and other handling

None stated.

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

ORSPEC Pharma Management Limited

PO BOX 59013

Mangere Bridge

Auckland 2151

9. DATE OF FIRST APPROVAL

24 September 2024

10. DATE OF REVISION OF THE TEXT

24 September 2024

SUMMARY TABLE OF CHANGES