PRODUCT MONOGRAPH

NORLUTATE®

(Norethindrone Acetate Tablets, USP)
5 mg

Progestin

ERFA
Canada 2012 Inc.

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NORLUTATE

(Norethindrone Acetate Tablets, USP)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of administration	Dosage Form/Strength	Clinically Relevant Non-medicinal Ingredients
oral	Tablet 5mg	Acacia, cornstarch, FD&C Red No. 3, FD&C Yellow No. 10, lactose, magnesium stearate, sugar and talc *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

NORLUTATE (Norethindrone Acetate) is indicated in the treatment of:

- Amenorrhea
- Endometriosis
- Abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer

Note: NORLUTATE (Norethindrone Acetate) should be prescribed only to women with intact uteri.

Patient subset

Geriatrics: No data is available.

Pediatrics: No data is available.

NORLUTATE (Norethindrone Acetate) has not been approved for use as Hormone Replacement Therapy (HRT) by menopausal or post-menopausal women.

CONTRAINDICATIONS

NORLUTATE (Norethindrone Acetate) is contraindicated in patients with :

- hypersensitivity to this drug or any of its components. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- active or past history of confirmed venous thromboembolism (such as deep vein thrombosis or pulmonary embolism) or active thrombophlebitis.
- active or past history of arterial thromboembolic disease (e.g. stroke, myocardial infarction, coronary heart disease).
- liver dysfunction or disease as long as liver function tests have failed to return to normal.
- known or suspected estrogen-dependent or progestin-dependant malignant neoplasia (e.g. endometrial cancer).
- known, suspected, or past history of breast cancer
- undiagnosed abnormal genital bleeding.
- partial or complete loss of vision due to ophthalmic vascular disease.
- known or suspected pregnancy.
- missed abortion (an abortion in which the fetus dies but is retained within the uterus for two months or longer).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Discontinue medication pending examination if there is a sudden partial or complete loss of vision or if there is sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

Because of the occasional occurrence of thrombophlebitis and pulmonary embolism in patients taking progestogens, the physician should be alert to the earliest manifestations of the disease. Care should be used when prescribing progestins to a population that may be predisposed to thrombotic disorders (e.g., past history of thrombotic events, thrombophilia, obesity, cardiovascular disease, prolonged immobilization).

Breast cancer

Some epidemiological studies of oral contraceptive users have reported an increased relative risk of developing breast cancer, particularly at a younger age and apparently related to duration of use.[3] These studies have predominately involved combined oral contraceptives and there is insufficient data to determine whether the use of progestin-only pills similarily increases the risk. Women with breast cancer should not use NORLUTATE (Norethindrone Acetate) because the role of female hormones in breast cancer has not been fully determined.

It is recommended that progestins not be given to women with existing breast cancer or those with a previous history of the disease (see **Contraindications**).

Other known risk factors for the development of breast cancer such as nulliparity, obesity, early menarche, late age at first full term pregnancy and at menopause should also be evaluated.

Endometrial hyperplasia and endometrial carcinoma

The role of progestin, when combined with estrogen, is to prevent endometrial hyperplasia/carcinoma in women with intact uteri.

Although the evidence is based on small numbers of women, the results of studies on progestogens suggest that women who use progestogen-only contraceptives have a reduced risk for endometrial cancer. It is unclear whether NORLUTATE (Norethindrone Acetate) provides protection against endometrial cancer.

Ovarian cancer

Some recent epidemiologic studies have found that the use of hormone replacement therapy (*estrogen-alone* and *estrogen plus progestin* therapies), in particular for five or more years, has been associated with an increased risk of ovarian cancer.

A recent prospective cohort study done on Danish women aged 50 through 79 years from 1995 through 2005 concluded that regardless of the duration of use, the formulation, regimen, progestin type, and route of administration, hormone therapy was associated with an increased risk of ovarian cancer.

Cardiovascular

The results of the Heart and Estrogen/progestin Replacement Studies (HERS and HERS II) and the Women's Health Initiative (WHI) trial indicate that the use of *estrogen plus progestin* is associated with an increased risk of coronary heart disease (CHD) in postmenopausal women.[1,5,6] The results of the WHI trial indicate that the use of *estrogen-alone* and *estrogen plus progestin* is associated with an increased risk of stroke in postmenopausal women.[1, 2]

It is however unclear from the literature if progestin alone increases the probability of acquiring cardiovascular diseases.

WHI trial findings

In the combined *estrogen plus progestin* arm of the WHI trial, among 10,000 women over a one-year period, there were:

8 more cases of stroke (29 on combined HRT versus 21 on placebo)
7 more cases of CHD (37 on combined HRT versus 30 on placebo).[1]

In the *estrogen-alone* arm of the WHI trial of women with prior hysterectomy, among 10,000 women over a one-year period, there were/was:

12 more cases of stroke (44 on *estrogen-alone* therapy versus 32 on placebo)
no statistically significant difference in the rate of CHD.[2]

HERS and HERS II findings

In the Heart and Estrogen/progestin Replacement Study (HERS) of postmenopausal women with documented heart disease (n=2763, average age 66.7 years), a randomized placebo-controlled clinical trial of secondary prevention of coronary heart disease (CHD), treatment with 0.625 mg/day oral conjugated equine estrogen (CEE) plus 2.5 mg oral medroxyprogesterone acetate (MPA) demonstrated no cardiovascular benefit. Specifically, during an average follow-up of 4.1 years, treatment with CEE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the hormone-treated group than in the placebo group in year 1, but not during the subsequent years.[5]

From the original HERS trial, 2321 women consented to participate in an open label extension of HERS known as HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. After 6.8 years, hormone therapy did not reduce the risk of cardiovascular events in women with CHD.[6]

Blood pressure

Progestin intake can cause existing blood pressure levels to rise and can lead to mild, moderate or serious hypertension. Caution must be taken in case of persons already suffering from hypertension.

Endocrine and Metabolism

Glucose and lipid metabolism

A worsening of glucose tolerance and lipid metabolism has been observed in significant percentage of peri- and post-menopausal patients. Therefore, diabetic patients or those with a predisposition to diabetes should be observed closely to detect any alterations in carbohydrate or lipid metabolism, especially in triglyceride blood levels.

A decrease in glucose tolerance has been observed in a small percentage of patients on Estrogen/progestogen combination drugs. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving progestogen therapy.

Women with familial hyperlipidemias need special surveillance. Lipid-lowering measures are recommended additionally, before treatment is started.

Heme metabolism

Women with porphyria need special surveillance. NORLUTATE (Norethindrone Acetate) can induce attacks of porphyria. Abdominal pain is the most common symptom to look for. Other symptoms include tachycardia, hypertension, restlessness, fine tremors, excess sweating, nausea, vomiting, constipation, pain in the limbs, head, neck, or chest, muscle weakness, and sensory loss. If recurrence of porphyria is suspected NORLUTATE (Norethindrone Acetate) should be discontinued.

Calcium and phosphorus metabolism

Progestins may precipitate hypercalcemia. Progestins should be used with caution in patients with metabolic and malignant bone diseases associated with hypercalcemia and in patients with renal insufficiency.

Hypothyroidism

Patients who require thyroid hormone replacement therapy and who are also taking progestins should have their thyroid function monitored regularly to assure that thyroid hormone levels remain in an acceptable range (see **Drug-Laboratory Test Interactions**).

Other conditions

NORLUTATE (Norethindrone Acetate) contains lactose. In patients with rare hereditary galactose intolerance, lactase deficiency or glucose-galactose malabsorption, the severity of the condition should be taken into careful consideration before prescribing NORLUTATE (Norethindrone Acetate). The patient should be closely monitored.

Genitourinary

Vaginal bleeding

Abnormal vaginal bleeding, due to its prolongation, irregularity or heaviness, occurring during therapy should prompt appropriate diagnostic measures to rule out the possibility of uterine malignancy and the treatment should be re-evaluated.

Uterine leiomyomata

Pre-existing uterine leiomyomata may increase in size during estrogen use. Growth, pain or tenderness of uterine leiomyomata requires discontinuation of medication and appropriate investigation.

Hematologic

Venous thromboembolism

Available data indicate that use of progestin by postmenopausal women is associated with an increased risk of developing venous thromboembolism (VTE).

Generally recognized risk factors for VTE include a personal history, a family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic predisposition), severe obesity (body mass index > 30 kg/m^2) and systemic lupus erythematosus. The risk of VTE also increases with age and smoking.

Care should be used when prescribing progestins to a population that may be predisposed to thrombotic disorders.

Hepatic/Biliary/Pancreatic

Gallbladder diseases

The effects of progesterone on the sphincter of Oddi and the gallbladder may contribute to the greater prevalence of gallstones and biliary motility disorder among women.[7]

Jaundice

Caution is advised in patients with a history of liver and/or biliary disorders. If cholestatic jaundice develops during treatment, the treatment should be discontinued and appropriate investigations carried out.

Liver function tests

Liver function tests should be done periodically in subjects who are suspected of having hepatic disease. For information on endocrine and liver function tests, see **Monitoring and Laboratory Tests**.

Impaired liver function

Steroid hormones are metabolized by the liver; therefore, these drugs should be administered with caution in patients with impaired liver function.

Immune

Systemic lupus erythematosus

Particular caution is indicated in women with systemic lupus erythematosus. If signs of thromboembolism are present, NORLUTATE (Norethindrone Acetate) should be discontinued.

Neurologic

Cerebrovascular insufficiency

Patients who develop visual disturbances, classical migraine, transient aphasia, paralysis or loss of consciousness should discontinue medication.
Patients with a previous history of classical migraine and who develop a recurrence or worsening of migraine symptoms should be reevaluated.

Dementia

It is unclear from the literature if progestins alone increase the risk of having dementia

Epilepsy

Particular caution is indicated in women with epilepsy, as progestins may cause an exacerbation of this condition.

Opthalmologic

Discontinue medication pending examination if there is a sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia. If examination reveals papilledema or retinal vascular lesions, withdraw the medication.

Psychiatric

Patients who have a history of mental depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Renal

Fluid retention

Since NORLUTATE (Norethindrone Acetate) may cause some degree of fluid retention, conditions that might be influenced by this factor, such as asthma, or cardiac or renal dysfunction, require careful observation. If, in any of the above-mentioned conditions, a worsening of the underlying disease is diagnosed or suspected during treatment, the benefits and risks of treatment should be reassessed based on the individual case.

Sexual Function/Reproduction

Menopause

The age of the patient constitutes no absolute limiting factor although treatment with progestogens may mask the onset of the climacteric.

Special Populations

Pregnancy

NORLUTATE (Norethindrone Acetate) is contraindicated in pregnancy. There may be an increased risk of birth defects in children whose mothers take this drug during the first four months of pregnancy. If the patient is exposed to NORLUTATE (Norethindrone Acetate) during pregnancy or if she becomes pregnant while taking this drug, she should be apprised of the potential risk to the fetus. Additionally, progestational agents are not recommended as diagnostic tests for pregnancy.

Nursing Women

Detectable amounts of progestogens have been identified in the milk of mothers receiving them. The effect of this on the nursing infant has not been determined.

Monitoring and Laboratory Tests

Before NORLUTATE (Norethindrone Acetate) is administered, the patient should have a complete physical examination including a blood pressure determination. Breasts and pelvic organs should be appropriately examined and a Papanicolaou smear should be performed. Endometrial biopsy should be done only when indicated. Baseline tests should include

mammography, measurements of blood glucose, calcium, triglycerides and cholesterol, and liver function tests.
The first follow-up examination should be done within 3-6 months after initiation of treatment to assess response to treatment. Thereafter, examinations should be made at intervals at least once a year. Appropriate investigations should be arranged at regular intervals as determined by the physician.

The importance of regular self-examination of the breasts should be discussed with the patient.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

See **Warnings and Precautions** regarding potential induction of malignant neoplasms and adverse effects similar to those of oral contraceptives.

The following adverse reactions have been reported with estrogen/progestin combination in general:

Blood and lymphatic system disorders

Altered coagulation tests (see **Warnings and Precautions, Drug-Laboratory Tests Interactions**).

Cardiac disorders

Palpitations; increase in blood pressure (see **Warnings and Precautions**); coronary thrombosis.

Endocrine disorders

Increased blood sugar levels; decreased glucose tolerance.

Eye disorders

neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis. ; visual disturbances; steepening of the corneal curvature; intolerance to contact lenses.

Gastrointestinal disorders

Nausea; vomiting; abdominal discomfort (cramps, pressure, pain, bloating).

General disorders and administration site conditions

Fatigue; changes in appetite; changes in body weight (increase or decrease); change in libido.

Hepatobiliary disorders

Gallbladder disorder; asymptomatic impaired liver function; cholestatic jaundice.

Musculoskeletal and connective tissue disorders

Musculoskeletal pain including leg pain not related to thromboembolic disease (usually transient, lasting 3-6 weeks) may occur.

Nervous system disorders

Aggravation of migraine episodes; headaches; dizziness; neuritis.

Psychiatric disorders

Mental depression; nervousness; irritability

Renal and urinary disorders

Cystitis; dysuria; sodium retention; edema.

Reproductive system and breast disorders

Breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea ; vaginal itching/discharge; dyspareunia ; amenorrhea; endometrial hyperplasia; pre-menstrual-like syndrome; reactivation of endometriosis; changes in cervical erosion and amount of cervical secretion; breast swelling and tenderness.

Skin and subcutaneous tissue disorders

Chloasma or melasma, which may persist when drug is discontinued; erythema multiform; erythema nodosum; haemorrhagic eruption; loss of scalp hair; hirsutism and acne.

Vascular disorders

Isolated cases of: thrombophlebitis; thromboembolic disorders.

Post-Market Adverse Drug Reactions

The following adverse drug reactions have been documented: cerebral infarction, palpitations, hypersensitivity reactions, suppressed lactation, brain stem infarction, cardiac arrest, increased blood prolactin, transient ischemia, hypercholesterolemia.

DRUG INTERACTIONS

Overview

Physicians and health care providers should be made aware of other drug products concomitantly used by the patient, including herbal and natural products.

Drug-Drug interactions

The metabolism of progestogens may be increased by concomitant administration of compounds know to induce drug-metabolizing enzymes, specifically Cytochrome P450 enzymes. See Table 1 for a list of drugs that may decrease the efficacy of NORLUTATE (Norethindrone Acetate):

Table 1: Drug That May Decrease the Efficacy of Progestins

Class of Compound	Drug
Anticonvulsivants	Carbamazepine Ethosuximide Phenobarbital Phenytoin

	Primidone Lamotrigine
Antifungals	Griseufulvin
Sedatives and Hypnotics	Benzodiazepines Barbiturates Chloral hydrate Gluthethimide Meprobamate
Anti-Infectives	Rifampicin Rifabutin Nevirapine Efavirenz Tetracyclines Ampicillin Oxacillin Cotrimaxazole
Other Drugs	Bosentan

Cases of possible drug interaction between NORLUTATE (Norethindrone Acetate) and Cyclosporin as well as Norethisterine and Linezoid have been described.

HIV protease inhibitors and non-nucleoside Reverse Transcriptase Inhibitors (ex: Ritonavir and Nelfinavir) may increase or decrease the plasma levels of a progestin.

Concurrent administration of Cyclosporin and NORLUTATE (Norethindrone Acetate) has been reported to lead to increased plasma Cyclosporin levels and/or decreased plasma NORLUTATE (Norethindrone Acetate) levels.

When used in combination with cytotoxic drugs, it is possible that progestogens may reduce the haematological toxicity of chemotherapy.

Special care should be taken when progestogens are administered with other drugs which also cause fluid retention, such as NSAIDs and vasodilators.

Refer to Oral Contraceptives 1994, health Canada (adapted from Dickey RP, ed.: Managing Contraceptive Pill Patients, 5th edition, EMIS Inc. Medical Publishers 1987), for other possible drug interactions with estrogen/progestin products.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

It was found that some herbal products (e.g. St. John's wort) which are available as over-the-counter (OTC) products might interfere with steroid metabolism and therefore alter the efficacy and safety of estrogen/progestin products.

Drug-Laboratory Test Interactions

The results of certain endocrine and liver function tests may be affected by progestins products:

- increased prothrombin time and partial thromboplastin time; increased levels of fibrinogen and fibrinogen activity; increased coagulation factors VII, VIII, IX, X; increased norepinephrine-induced platelet aggregability; decreased antithrombin III;
- other binding proteins may be elevated in serum i.e., corticosteroid binding globulin (CBG), sex-hormone binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively; free or biologically active hormone concentrations are unchanged;
- increased serum triglycerides and phospholipids concentration;

In addition, the following laboratory results may be altered by the concomitant use of estrogens with progestogens: hepatic function; coagulation tests and increase in PBI (protein-bound iodine) and BEI (butanol-extractable iodine).

The results of the above laboratory tests should not be considered reliable unless therapy has been discontinued for two to four weeks.

The pathologist should be informed that the patient is receiving progestin when relevant specimens are submitted.

The pregnanediol determination may be altered by the use of progestogens.

DOSAGE AND ADMINISTRATION

Dosing considerations

Adapt dosage to the specific indications and therapeutic response of the individual patient. This dosage schedule assumes the interval between menses to be 28 days.

Recommended Dose and Dosage Adjustment

Amenorrhea, abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology: 2.5 to 10 mg starting with the fifth day of the menstrual cycle and ending on the 25th day.

Endometriosis: Initial daily dose of 5 mg for 2 weeks with increments of 2.5 mg/day every 2 weeks until 15 mg/day is reached. Therapy may be held at this level from 6 to 9 months or until breakthrough bleeding demands temporary termination.

Take with food or after a meal to prevent stomach upset.
A study has shown that systemic exposure to Norethindrone Acetate increased by 27% when administered with a high-fat meal but the clinical significance of this is not known.

Missed Dose

If a dose is missed, patient should take it as soon as they remember. If it is near the time of the next dose, skip the missed dose and resume your usual dosing schedule. Do not double the dose to catch up.

Administration

NORLUTATE (Norethindrone Acetate) is intended for oral administration only.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre

Symptoms of overdose

Progestin (e.g. Norethindrone acetate) overdosage has been characterized by depressed mood, tiredness, acne and hirsutism.

Treatment of overdose

Symptomatic treatment should be given.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

NORLUTATE (Norethindrone Acetate) transforms proliferative endometrium into secretory endometrium.

Endometriosis is an estrogen-dependent disorder in women of reproductive age that is characterized by the presence of endometrial-like tissue outside the uterine lining. The putative mechanism of action of NORLUTATE (Norethindrone Acetate) in the treatment of endometriosis is by the inhibition of pituitary gonadotropin production and thereby decrease in gonadotropin section, which leads to endometrial decidualization, atrophy of endometriotic implants and decrease in circulating estrogen levels.

Progestin compounds enhance cellular differentiation and generally oppose the actions of estrogens by decreasing estrogen receptor levels, increasing local metabolism of estrogens to less active metabolites, or inducing gene products that blunt cellular responses to estrogen.

NORLUTATE (Norethindrone Acetate) may also demonstrate some estrogenic, anabolic or antiandrogenic activity but these activities should not be relied upon.

Any possible influence of prolonged progestogen therapy on pituitary, ovarian, adrenal, hepatic or uterine functions awaits further study.

Pharmacokinetics

Absorption

Norethindrone acetate is rapidly absorbed, with maximum plasma concentration of Norethindrone generally occurring at about 2 hours post-dose.[16]

Distribution

Norethindrone Acetate is 36% bound to sex hormone-binding globulin (SHBG) and 61% bound to albumin. Volume of distribution of Norethindrone Acetate is about 4 L/kg.

Metabolism

Norethindrone acetate is completely and rapidly deacetylated to Norethindrone (NET) after oral administration, and the disposition of Norethindrone Acetate is indistinguishable from that of orally administered Norethindrone. Norethindrone Acetate undergoes extensive biotransformation, primarily via reduction, followed by sulfate and glucuronide conjugation. The majority of metabolites in the circulation are sulfates, with glucuronides accounting for most of the urinary metabolites.[17]

Excretion

Plasma clearance value for Norethindrone Acetate is approximately 0.4 L/hr/kg. Norethindrone Acetate is excreted in both urine and feces, primarily as metabolites. The mean terminal elimination half-life of Norethindrone Acetate following a single dose administration of NORLUTATE (Norethindrone Acetate) is approximately 9 hours.

Special Populations and Conditions

Renal insufficiency

In premenopausal women with chronic renal failure undergoing peritoneal dialysis who received multiple doses of an oral contraceptive containing ethinyl estradiol and Norethindrone Acetate, plasma Norethindrone Acetate concentration was unchanged compared to concentrations in premenopausal women with normal renal function.

STORAGE AND STABILITY

Store at controlled room temperature (15 - 30^{o}C).
Keep in a safe place out of the reach of children

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each cylindrical, flat, salmon-coloured tablet, beveled, scored on one side contains : Norethindrone Acetate 5 mg.

Each grooved, salmon-coloured, slightly mottled tablet, debossed "PD" on one side contains: Norethindrone Acetate 5 mg.

Nonmedicinal ingredients: acacia, cornstarch, FD&C Red No. 3, FD&C Yellow No. 10, lactose, magnesium stearate, sugar and talc. Sodium: 0.30 mg. Gluten-, paraben-, sulfite- and tartrazine-free. Energy: 1.4 kJ (0.34 kcal).

NORLUTATE (Norethindrone Acetate) is for oral administration only. NORLUTATE (Norethindrone Acetate) is available in 5mg tablet strength in bottles of 30 tablets each.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

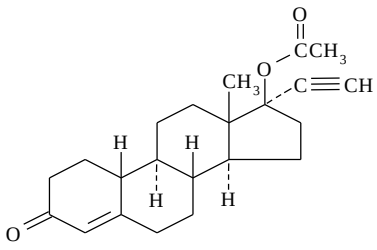
Proper Name: Norethindrone Acetate

Chemical Name: 19-Norpregn-4-en-20-yn-3-one, 17-(acetyloxy)-, (17∀).

Empirical Formula: $C_{22}H_{28}O_3$

Molecular Weight: 340.46

Structural Formula:



Relevant physicochemical properties: synthetic, orally active progestin that is the acetic acid ester of Norethindrone. It is a white or creamy white, crystalline powder.

CLINICAL TRIALS

Norethindrone Acetate was developed by Junkmann in 1959. A cumulative dose of 10-40 mg of Norethindrone Acetate was given to oestrogen-primed castrated women over a period of 10 days in order to produce a full secretory-phase endometrium.

Foss *et al* treated 90 patients with Norethindrone and Norethindrone Acetate with various pathologies including primary and secondary amenorrhoea, oligomenorrhoea, some dysmenorrhoea and a larger series of menometrorrhagia cases. Table 2 shows the number of patients treated in each group.

A total of 69 patients were treated with Norethindrone and 56 patients treated with Norethindrone Acetate as shown in Table 2. Some patients received Norethindrone alone or Norethindrone Acetate alone, while others were treated with both steroids at different times. Norethindrone Acetate was given to 10 patients with secondary amenorrhoea for a total of 22 cycles for all the patients. Norethindrone Acetate was given in doses of 2, 4, or 6 mg. daily, for 10 days. A secretory phase was observed in the endometrium in all patients except one.

In the whole group of 38 cases of menometrorrhagia treated with Norethindrone Acetate given various doses over a 10-day period, control of menstrual loss was obtained in 75% of 205 cycles for all the patients. Foss *et al* concluded that the control of prolonged excessive regular or irregular menstruation was effective with Norethindrone and Norethindrone Acetate..[10]

Table 2: Number of Patients Treated[10]

Norethindrone			Norethindrone Acetate		
	No. of patients	No. of cycles		No. of patients	No. of cycles
Menorrhagia	26	101	Menorrhagia	38	205
Primary amenorrhoea	7	76	Secondary amenorrhoea	10	22
Secondary amenorrhoea	25	320	Others	8	20
Oligomenorrhoea	5	23			
Dysmenorrhoea	6	15			
Total	69	535	Total	56	247

Forty-one patients with pelvic endometriosis form the basis of the study from Snaith et al. In 18 cases, initial diagnoses were made via laparotomy, without previous hormone therapy or surgery: treatment post-laparotomy and conservative surgery ranged from 800 to 6,000 mg of Norethindrone Acetate in total over a period of 7-8 weeks. All cases improved but how much of the improvement was the result of the conservative surgery (with extirpation of as much endometriosis as possible) is debatable.[11]

Bishop *et al* described the use of Norethindrone Acetate that was administered to 20 dysmenorrhoeic women in 102 cycles for all the patients, with the object of inhibiting ovulation and thereby causing painless uterine bleeding. Pain was inhibited in 73% to 90% of patients with dosages of Norethindrone Acetate ranging from 15mg to 20 mg daily. [12]

In a study to evaluate the efficacy, safety and tolerability of an estrogen-progestogen combination versus a low-dose Norethindrone Acetate for the treatment of symptomatic rectovaginal endometriotic post-surgical persistent pain, Vercellini *et al.* took 90 women with recurrent moderate to severe pain after unsuccessful conservative surgery for symptomatic rectovaginal endometriosis. Patients were treated with Norethindrone Acetate, 2.5 mg/day or with continuous treatment of oral ethinyl E2 in combination with Cyproterone Acetate. Five patients in the Norethindrone Acetate cohort were withdrawn due to adverse events, six patients were withdrawn due to treatment inefficacy and one patient, due to loss of follow-up. According to an intention-to-treat analysis, 28 out of 45 patients (62%) in the ethinyl E2 in combination with Cyproterone Acetate cohort and 33 out of 45 patients (73%) in the Norethindrone Acetate cohort were satisfied with the received treatment. Vercellini *et al*. concluded that low-dose Norethindrone Acetate could be considered an effective, tolerable and inexpensive first-choice medical alternative to repetitive surgery for treatment of symptomatic rectovaginal endometriotic lesions.[13]

In a study by Muneyyirci-Delale *et al,* 52 women with symptomatic and laparoscopically confirmed endometriosis were given Norethindrone Acetate in order to evaluate its efficacy. Norethindrone Acetate was continued for 6 months to > 1 year and was started at the beginning of the menstrual cycle at a daily dose of 5mg which was increased by 2.5 mg up to 20mg/day until amenorrhoea was achieved. Chronic pelvic pain and dymenorrhoea regressed in 89% and 92% respectively. At the end of treatment, 94% of women had few or no symptoms. Breakthrough bleeding was experienced by 30 of the 52 patients. Three patients dropped out because of inefficacy and one other because of breast tenderness.[18]

DETAILED PHARMACOLOGY

Please refer to **ACTION AND CLINICAL PHARMACOLOGY** section for more information.

TOXICOLOGY

Animal studies

High-dose administration of various estrogenic and progestogenic agents alone or in combination to susceptible strains of rodents has been shown to increase the incidence of specific tumors in

the pituitary, uterus, breast, ovary, and liver. Administration of Norethindrone Acetate alone to rodents at several multiples of the human dose resulted in no treatment related mortality, hematological changes or behavioural changes. However, Norethindrone Acetate appears to cause cholestasis in rats. Rats given Norethindrone Acetate at 40 mg/kg-day for 5 days showed a 34% reduction in total bile flow.

Some beagle dogs treated with medroxyprogesterone acetate developed mammary nodules. Although nodules occasionally appeared in control animals, they were intermittent in nature whereas nodules in treated animals were larger and more numerous, and persisted. The laboratory dog, particularly the beagle, has unique endocrine properties such that caution should be exercised when extrapolating the results to human exposures. Progestins stimulate the production of growth hormone, which in turn leads to an increase in the number of palpable mammary tumors. Their significance in respect to humans has not been established.

The results of long-term monkey studies indicate that overall, long-term treatment with high doses of progestins fails to produce significant signs of systemic toxicity or tumor development. There were no hematologic or target organ pathologic findings attributable to steroid treatment. Only an occasional mammary nodule or local mammary hyperplasia was observed in monkeys given high doses of progestin for a period of 5 to 10 years.[19]

Human

Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. One study estimated a 4.7 fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal test for pregnancy, or attempted treatment for threatened abortion).[20] Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 in 1,000.

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IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

NORLUTATE
(NORETHINDRONE ACETATE)
TABLETs, USP

This leaflet is part III of three-part ``Product Monograph`` published when NORLUTATE was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about NORLUTATE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Norlutate is indicated in:

- lack of menstruation (amenorrhea)
- abnormal bleeding of the uterus (womb) due to hormonal imbalance (if you don't have other diseases and if you don't have cancer of the uterus)
- endometriosis.

Norlutate should be prescribed only to women with intact uteri.

Norlutate should be used only under the supervision of a doctor, with regular follow-up at least once a year to identify side effects associated with its use. Your first follow-up visit should be within 3 to 6 months of starting treatment. Your visit may include a blood pressure check, a breast exam, a Pap smear and pelvic exam. Your doctor may recommend some blood tests.

Norlutate is not intended for use as hormone replacement therapy (HRT) for treating menopausal and post-menopausal symptoms.

What it does:

NORLUTATE is similar to the progesterone hormones naturally produced by the body.

When it should not be used:

Do not take NORLUTATE if:

- You have hypersensitivity to this drug or any of its components.
- You have or have had problems such as stroke, heart attack, or coronary heart disease.
- You have liver disease and liver function tests have failed to return to normal.
- You have known or suspected endometrial cancer or any other cancer which is sensitive to estrogens or progestins.
- You have known, suspected or history of breast cancer.
- You have undiagnosed genital bleeding.
- You have a known or suspected pregnancy
- You had or have confirmed venous thrombo-embolism (blood clots) or active thrombophlebitis (inflammation of the veins).
- You had partial or complete loss of vision due to blood vessel disease in the eye.
- You suffer from missed abortion (an abortion in which the fetus dies but is retained within the uterus).

What the medicinal ingredient is:

Norethindrone acetate

What the non medicinal ingredient are:

Acacia, cornstarch, FD&C Red No. 3, FD&C Yellow No. 10, lactose, magnesium stearate, sugar and talc

What dosage forms it comes in:

Each cylindrical, flat, salmon-coloured tablet, beveled, scored on one side contains : Norethindrone Acetate 5 mg.
Each grooved, salmon-coloured, slightly mottled tablet, debossed "PD" on one side contains: Norethindrone Acetate 5 mg.

WARNING AND PRECAUTIONS

Serious Warnings and Precautions

Discontinue medication and consult your physician immediately if there is a sudden partial or complete loss of vision or if there is sudden onset of proptosis (bulging of the eye), diplopia (double vision), or migraine.

You might have an increase risk of having thrombophlebitis and pulmonary embolism while taking this medication

Breast Cancer

Some epidemiological studies of oral contraceptive users have reported an increased relative risk of developing breast cancer, particularly at a younger age and apparently related to duration of use. These studies have predominately involved combined oral contraceptives and there is insufficient data to determine whether the use of progestin-only pills like Norlutate similarily increases the risk. If you have or had breast cancer you should not use Norlutate before discussing with your physician since the role of this pill in breast cancer has not been fully determined.

Regular breast examinations by a doctor and regular breast self-examinations are recommended for all women. You should review technique for breast self-examination with your doctor.

Overgrowth of the lining of the uterus and cancer of the uterus

You should discuss progestin therapy and risk factors for endometrial hyperplasia and endometrial carcinoma with your doctor. You should also report any unexpected or unusual vaginal bleeding to your doctor.
If you have had your uterus removed, you are not at risk of developing endometrial hyperplasia or endometrial carcinoma. Progestin therapy is therefore not generally required in women who have had a hysterectomy.

Ovarian Cancer

In some studies, the use of *estrogen-alone* and *estrogen plus progestin* therapies for 5 or more years has been associated with an increased risk of ovarian cancer.

Heart Disease and Stroke

It is unclear from the literature if progestin alone increases the risk of having cardiovascular diseases.

Abnormal Blood Clotting

The results of the WHI trial indicated an increased risk of blood clots in the lungs and large veins in post-menopausal women taking combined estrogen plus progestin compared to women taking placebo.

Available data indicate that use of progestin by postmenopausal women is associated with an increased risk of developing blood clots.

The risk of blood clots also increases with age, if you or a family member has had blood clots, if you smoke or if you are severely overweight. The risk of blood clots is also temporarily increased if you are immobilized for long periods of time and following major surgery. You should discuss risk factors for blood clots with your doctor since blood clots can be life-threatening or cause serious disability.

Dementia

It is unclear from the literature if progestin alone increases the risk of having dementia

BEFORE you use NORLUTATE talk to your doctor or pharmacist if you:

- have a history of allergy or intolerance to any medications or other substances
- have a personal history of breast disease (including breast lumps) and/or breast biopsies, or a family history of breast cancer
- have experienced any unusual or undiagnosed vaginal bleeding
- have a history of uterine fibroids or endometriosis
- have a history of liver disease, jaundice (yellowing of the eyes and/or skin) or itching related to estrogen use or during pregnancy
- have a history of migraine headache
- have high blood pressure
- have a personal or family history of blood clots, or a personal history of heart disease or stroke
- have kidney disease, asthma or epilepsy (seizures)
- have a history of bone disease (this includes certain metabolic conditions or cancers that can affect blood levels of calcium and phosphorus)
- have diabetes
- have porphyria (a disease of blood pigment)
- have high cholesterol or high triglycerides
- are pregnant or may be pregnant
- have had a hysterectomy (surgical removal of the uterus)
- smoke
- have lupus
- have or have had a history of depression
- have or have had problems with your gallbladder
- are breastfeeding

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking any other medications, including prescription medications, over-the-counter medications, vitamins or herbal products.

Drugs that may interact with Norlutate include:

- drugs used for the treatment of epilepsy
- drugs used for the treatment of infection
- drugs used for the treatment of pulmonary hypertension (bosentan)
- sedative and hypnotics (bezodiazepines, barbiturates)
- cyclosporin

PROPER USE OF THIS MEDICATION

Usual dose:

NORLUTATE is taken by mouth with food or after a meal to prevent stomach upset.

Follow your doctor`s orders or the directions on the label.

This dosage schedule assumes that the interval between your menstrual periods is 28 days.

Amenorrhea or Abnormal uterine bleeding:
2.5 to 10 mg starting with the fifth day of your menstrual cycle and ending on the 25th day.

Endometriosis:
Initial daily dose: 5 mg for 2 weeks with increments of 2.5 mg/day every 2 weeks until 15 mg/day is reached. The treatment may continue for 6 to 9 months or until breakthrough bleeding stops.

Overdose

If you take too much NORLUTATE you could have depressed mood, tiredness, acne and hirsutism.

In case of a suspected drug overdose, contact your health care practitioners, or your regional Poison Control Center.

Missed dose

If you missed a dose, you should take it as soon as you remember. If it is near the time of the next dose,

skip the missed dose and resume your usual dosing schedule.

Do not double the dose to catch up.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects include swelling of ankles or feet, absent menstrual period and mild headache. These effects should disappear as your body adjusts to the medication. If they persist, become bothersome or increase in severity, inform your doctor. If an absent menstrual period persists please consult your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/possible side effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Abdominal pain, nausea or vomiting		✔	
	Headache	✔		
	Persistent sad mood			✔
	Breakthrough bleeding, Change in menstrual flow, spotting or unexpected vaginal bleeding		✔	
	Changes in weight (increase or decrease), fluid retention	✔		
Uncommon	Changes in skin pigmentation, Itching, Rash			✔
	sleeplessness, or irritability	✔		
	Yellowing of the skin or eyes (jaundice)			✔
	Crushing chest pain or chest heaviness			✔
	Pain or swelling in the leg			✔
	Breast lump		✔	
	Sharp pain in the chest, coughing blood or sudden shortness of Breath			✔
	Sudden partial or complete loss of vision			✔
	Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech or weakness or numbness in an arm or leg			✔

This is not a complete list of side effects. For any unexpected effects while taking NORLUTATE, contact your doctor or pharmacist.

HOW TO STORE IT

Store at controlled room temperature (15 - 30°C).

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
    - Fax toll-free to 1-866-678-6789, or
    - Mail to:
      Canada Vigilance Program
      Health Canada
      Postal Locator 0701D
      Ottawa, Ontario
      K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph prepared for health professionals can be found at http://www.ECI2012.net or by contacting the sponsor, ERFA Canada 2012 Inc. at 1-888-922-3133.

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