PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr NORLUTATE®

Norethindrone Acetate Tablets U.S.P.

Tablets, 5 mg, for oral administration

Progestin

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RECENT MAJOR LABEL CHANGES

N/A	

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

NORLUTATE (norethindrone acetate tablets U.S.P.) is indicated for 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

NORLUTATE should be prescribed only to women with intact uteri.

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

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

- Norethindrone acetate is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- 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).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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).

4 DOSAGE AND ADMINISTRATION

4.1 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.

4.2 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.

4.4 Administration

NORLUTATE is intended for oral administration only.

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.

4.5 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.

5 OVERDOSAGE

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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 - Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet 5 mg	Acacia, cornstarch, FD&C Red No. 3, FD&C Yellow No. 10, lactose, magnesium stearate, sugar and talc

Grooved, salmon-coloured, slightly mottled tablet, debossed “PD” on one side.

Sodium: 0.30 mg. Gluten-, paraben-, sulfite- and tartrazine-free. Energy: 1.4 kJ (0.34 kcal).

NORLUTATE is available in 5mg tablet strength in bottles of 30 tablets each.

7 WARNINGS AND PRECAUTIONS

Please see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**.

Carcinogenesis and Mutagenesis

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 similarly increases the risk. Women with breast cancer should not use NORLUTATE 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 2 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 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. 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.

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).

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.

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.

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.

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 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 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 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 . 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 should be discontinued.

Monitoring and Laboratory Tests

Before NORLUTATE 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.

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.

Ophthalmologic

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 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.

Reproductive Health: Female and Male Potential

- **Fertility**

  No data are available.

- **Function**

  Menopause

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

7.1 Special Populations

7.1.1 Pregnant Women

NORLUTATE 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 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.

7.1.2 Breast-feeding

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.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

See 7 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 7 WARNINGS AND PRECAUTIONS, 9.7 Drug-Laboratory Test Interactions).
Cardiac disorders	Palpitations; increase in blood pressure (see 7 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.

8.5 Post-Market Adverse 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.

9 DRUG INTERACTIONS

9.2 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.

The metabolism of progestogens may be increased by concomitant administration of compounds know to induce drug-metabolizing enzymes, specifically Cytochrome P450 enzymes.

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.

9.3 Drug-Behavioural Interactions

The risk of VTE increases with smoking.

9.4 Drug-Drug Interactions

Table 2 - Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Anticonvulsivants, such as carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone, lamotrigine	T	May decrease the efficacy of NORLUTATE	Caution is warranted and therapeutic concentration monitoring is recommended
Antifungals, such as griseufulvin	T	May decrease the efficacy of NORLUTATE	Caution is warranted and therapeutic concentration monitoring is recommended
Sedatives and hypnotics, such as benzodiazepines, barbiturates, chloral hydrate, gluthethimide, meprobamate	T	May decrease the efficacy of NORLUTATE	Caution is warranted and therapeutic concentration monitoring is recommended
Anti-Infectives, such as Rifampicin, Rifabutin, Nevirapine, Efavirenz, Tetracyclines, Ampicillin, Oxacillin, Cotrimaxazole	T	May decrease the efficacy of NORLUTATE	Caution is warranted and therapeutic concentration monitoring is recommended
Bosentan	T	May decrease the efficacy of NORLUTATE	Caution is warranted and therapeutic concentration monitoring is recommended
Cyclosporine	C	Concurrent administration of Cyclosporin and NORLUTATE has been reported to lead to increased plasma Cyclosporin levels and/or decreased plasma NORLUTATE levels.	Caution is warranted and therapeutic concentration monitoring is recommended
Norethisterine	C	Cases of possible drug interaction with NORLUTATE have been described	Caution is advised
Linezolid	C	Cases of possible drug interaction with NORLUTATE have been described	Caution is advised

Proper/Common name	Source of Evidence	Effect	Clinical comment
HIV protease inhibitors and non-nucleoside Reverse Transcriptase Inhibitors, such as ritonavir and nelfinavir	T	May increase or decrease the plasma levels of progestins	Caution is warranted and therapeutic concentration monitoring is recommended
Cytotoxic drugs	T	Progestogens may reduce the haematological toxicity of chemotherapy	Caution is warranted and therapeutic concentration monitoring is recommended
NSAIDs	T	Cumulative effect on fluid retention	Special care should be taken when progestogens are administered with other drugs which also cause fluid retention
Vasodilators	T	Cumulative effect on fluid retention	Special care should be taken when progestogens are administered with other drugs which also cause fluid retention

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 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.

9.7 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.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

NORLUTATE 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 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.

10.2 Pharmacodynamics

NORLUTATE 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.

10.3 Pharmacokinetics

Absorption

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

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.

Elimination

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 is approximately 9 hours.

Special Populations and Conditions

- **Pregnancy and Breast-feeding**

  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). 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.

- **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.

11 STORAGE, STABILITY AND DISPOSAL

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

Keep in a safe place out of the reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

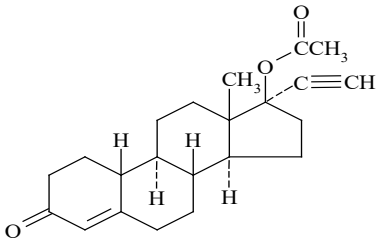
Drug Substance

Proper name: Norethindrone Acetate

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

Molecular formula and molecular mass: $C_{22}H_{28}O_3$ 340.46 g/mol

Structural formula:



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

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Treatment of amenorrhea, endometriosis and abnormal uterine bleeding

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.

Table 3 - Number of Patients Treated

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

14.2 Study Results

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.

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.

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.

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.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: 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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr NORLUTATE®

norethindrone acetate tablets U.S.P.

Read this carefully before you start taking **NORLUTATE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **NORLUTATE**.

Serious Warnings and Precautions

- **Eye problems:** NORLUTATE may cause eye problems such as sudden partial or complete loss of vision, sudden bulging of the eyes, double vision, or migraines. Stop taking NORLUTATE and tell your healthcare professional **right away** if you experience these symptoms.

- **Blood clots:** They can occur with NORLUTATE use. Blood clots can happen in your veins, especially in the legs, (thrombophlebitis) or your lungs (pulmonary embolism). Stop taking NORLUTATE and **seek immediate medical help** if you experience any of the following symptoms:
  - Swelling and redness along a vein, which is extremely tender or painful when touched.
  - Sudden shortness of breath, chest pain that may increase with deep breathing, coughing or coughing up blood.

What is NORLUTATE used for?

NORLUTATE is used only in adult women with an intact womb (uterus) to treat:

- the absence of menstrual periods (amenorrhea).
- abnormal bleeding of the uterus due to a hormonal imbalance. For these patients, the bleeding is not caused by other diseases such as benign growths in the uterus (called fibroids) or uterine cancer.
- endometriosis, a condition in which the tissue that forms the lining of the uterus (endometrium) grows in other parts of the body. This can cause pain when you have your period, during other times of the month or during sex.

NORLUTATE is not intended for use as hormone replacement therapy (HRT) for treating symptoms of menopause or post-menopause.

How does NORLUTATE work?

NORLUTATE is a type of hormone called progestin. It is similar to the progesterone hormone that is naturally produced by your body. It works by:

- stopping the normal growth of the endometrium during the menstrual cycle. This helps to treat endometriosis by shrinking endometrium-like tissue found outside the uterus.
- signaling hormone changes in the uterus to restore normal menstrual periods. This helps to treat the absence of periods or abnormal bleeding of the womb due to a hormonal imbalance.

What are the ingredients in NORLUTATE?

Medicinal ingredients: Norethindrone acetate

Non-medicinal ingredients: Acacia, cornstarch, FD&C Red No. 3, FD&C Yellow No. 10, lactose, magnesium stearate, sugar and talc

NORLUTATE comes in the following dosage forms:

Tablets; 5 mg.

Do not use NORLUTATE if:

- you are allergic to norethindrone acetate or to any other ingredients in NORLUTATE.
- you have or have had blood clots in the legs, lungs, eyes or any other part of the body, or currently suffer from inflammation of the veins (thrombophlebitis).
- you have or have had a stroke, heart attack, or coronary artery disease.
- you have liver disease and liver function tests have failed to return to normal.
- you have or think you may have a tumour associated with the use of estrogen or progestin containing products (e.g., cancer of the lining of the uterus or the ovaries).
- you have, have had or think you may have breast cancer.
- you have unusual vaginal bleeding without a known reason.
- you have partial or complete loss of vision due to a blood vessel disease of the eye.
- you are pregnant or think you might be pregnant.
- you suffer from a missed abortion (also known as a missed miscarriage). It is a miscarriage in which the fetus is no longer alive, but the body does not recognize the pregnancy loss or expel the pregnancy tissue.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take NORLUTATE. Talk about any health conditions or problems you may have, including if you:

- have risk factors for breast cancer such as:
  - you have never given birth to a child.
  - you are overweight.
  - you had your first period at an early age.
  - you had your first child later in life.
  - you are in menopause (you haven't experienced a period for a year).
- are in post-menopause (you haven't experienced a period for more than a year).
- have heart disease.
- have high blood pressure.
- have diabetes or have high blood sugar levels as NORLUTATE may worsen your tolerance to glucose (sugar).
- have high blood cholesterol or triglyceride levels, including if you have familial hyperlipidemia (a disorder where high levels of fat in the blood are passed down through families).

- have porphyria (a rare blood disorder passed down through families). NORLUTATE can bring about a porphyria attack.
- have kidney problems.
- have bone problems (e.g., osteoporosis, bone tumours), or other conditions that can affect blood calcium and phosphorus levels.
- have thyroid problems.
- have one of the following rare hereditary conditions as NORLUTATE contains lactose:
  - galactose intolerance
  - lactase deficiency
  - glucose-galactose malabsorption
- have benign growths in your uterus (called fibroids).
- have a family history, or have risk factors for blood clots (venous thromboembolism) such as:
  - you are severely overweight (body mass index greater than 30).
  - your blood forms clots easily (thrombophilia).
  - you have heart or blood vessel problems.
  - you have lupus (an autoimmune disease).
  - you had prolonged bed rest, or immobility.
  - your age.
  - you are a smoker.
- have liver or gallbladder problems.
- have a history of migraines.
- have dementia.
- have epilepsy (seizures). NORLUTATE may worsen your condition.
- have or have a history of depression.
- have asthma.
- are breastfeeding or are planning to breastfeed.

Other warnings you should know about:

Check-ups and testing: NORLUTATE should only be used under the supervision of a healthcare professional, with regular check-ups to identify side effects related to its use. Before you start taking NORLUTATE, your healthcare professional will ask you some questions about your personal health history and that of your close relatives. They will also conduct a complete physical exam, which includes:

- A blood pressure check.
- A breast exam, including a mammography.
- A pelvic exam, including a Pap smear.
- A biopsy of the lining of the uterus, if necessary.
- Blood tests to monitor:
  - Your blood glucose (sugar) levels
  - Your blood cholesterol and triglyceride levels (types of fats)
  - Your blood calcium levels
  - The health of your thyroid or liver, if necessary

The first follow-up exam should be done 3 to 6 months after starting treatment with NORLUTATE. After this, exams should be done at least once a year.

Breast cancer: Some studies have shown that the risk of breast cancer increases in women taking birth control pills, especially at a younger age. The risk was also linked to how long the birth control pills were taken. These studies mainly involved birth control pills containing both estrogen and progestin. It is not known whether the use of progestin-only pills, such as NORLUTATE, may have similar risks.

Talk to your healthcare professional for advice and instructions on how to self-examine your breasts. Check your breasts often while you are taking NORLUTATE. See your healthcare professional **right away** if you notice any changes such as:

- Dimpling or sinking of the skin
- Changes in the nipple
- Any lumps you can see or feel

If you detect any new masses on your breasts while taking NORLUTATE, you should also talk to your healthcare professional. Your healthcare professional should do a breast exam at least once per year.

Ovarian cancer: Some studies have shown that the risk of ovarian cancer increases in women receiving hormone replacement therapy (HRT), especially for 5 or more years. These studies included estrogen-only and estrogen plus progestin therapies.

Your healthcare professional should do a pelvic exam at least once a year. When ovarian cancer first develops, it might not cause any noticeable symptoms. If you experience some of the following symptoms, tell your healthcare professional right away:

- Abdominal bloating or swelling
- Quickly feeling full when eating
- Weight loss
- Discomfort in the pelvic area
- Lack of energy
- Back pain
- Changes in bowel movements
- Frequent need to urinate

Unusual vaginal bleeding: Tell your healthcare professional **right away** if you ever have unusual vaginal bleeding while taking NORLUTATE. This includes:

- Irregular bleeding or spotting (unexpected bleeding that can happen between your normal menstrual periods)
- Longer or heavier than usual menstrual periods

These may be signs of benign growths in your uterus (called fibroids) or cancer of the uterus.

You should discuss progestin therapy and risk factors for overgrowth of the lining of the uterus and cancer of the uterus with your healthcare professional. If you have had your uterus removed, you are not at risk of developing these conditions. Progestin therapy, such as NORLUTATE, is usually not needed in women who have had a hysterectomy (surgery to remove the uterus).

Heart disease and stroke: It is unclear if the use of progestin-only pills, such as NORLUTATE, increases the risk of heart disease and stroke. However, if you develop vision changes, migraines or worsening of migraines, temporary speech problems, loss of muscle function (paralysis) or fainting, stop taking

NORLUTATE and tell your healthcare professional **right away**. These may be signs that your brain is not getting enough blood flow or that you are having a stroke.

Gallbladder problems: NORLUTATE may cause gallbladder problems such as gallstones and biliary motility issues (gallbladder isn't contracting and ejecting bile as it should).

Dementia: It is unclear if progestin alone, such as NORLUTATE, increases the risk of having dementia.

Pregnancy: You should not take NORLUTATE during pregnancy. There may be an increased risk of birth defects in children whose mothers have taken this medicine during the first 4 months of pregnancy. If you discover that you are pregnant while taking NORLUTATE, tell your healthcare professional **right away**. They will discuss with you the potential risks to your unborn baby.

Breastfeeding: NORLUTATE passes into breastmilk. It is not known if it can harm a breastfed baby. Therefore, it is not recommended to breastfeed while taking NORLUTATE. Talk to your healthcare professional about the best way to feed your baby during this time.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with NORLUTATE:

- Other medications containing norethindrone (or also called norethisterone)
- Medicines known as "corticosteroids", used to treat inflammation
- Medicines used to treat HIV/AIDS (e.g., ritonavir, nelfinavir, nevirapine, efavirenz)
- Medicines that may cause fluid retention such as:
  - Non-steroidal inflammatory drugs (NSAIDs), used to treat pain, inflammation and fever (e.g., ibuprofen, naproxen, acetylsalicylic acid)
  - Medicines that open your blood vessels, used to treat high blood pressure, chest pain and other heart conditions
- Medicines used to treat seizures (e.g., carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone, lamotrigine)
- Medicines used to treat fungal infections (e.g., griseofulvin)
- Medicines used to treat bacterial infections (e.g., rifampicin, rifabutin, tetracyclines, ampicillin, oxacillin, trimethoprim/sulfamethoxazole, linezolid)
- Medicines that may enhance drowsiness or are used to help with sleeping such as sedatives and hypnotics (e.g., benzodiazepines, barbiturates, chloral hydrate, glutethimide, meprobamate)
- Cytotoxic medicines, used during chemotherapy in the treatment of cancer
- Cyclosporine, used to suppress the immune system
- Bosentan, used to treat high blood pressure in the lungs
- Smoking
- Certain herbal and natural products such as St. John's wort

How to take NORLUTATE:

- NORLUTATE is taken by mouth with food or after a meal to prevent stomach upset.
- Take NORLUTATE exactly as your healthcare professional has told you.

Usual dose:

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

- **To treat the absence of menstrual periods or abnormal bleeding from the uterus:**

  2.5 to 10 mg per day starting with the fifth day of your menstrual cycle and ending on the 25th day.

- **To treat endometriosis:**

  The starting dose is 5 mg per day for the first 2 weeks of treatment. Your daily dose will be increased by 2.5 mg every 2 weeks until you reach a daily dose of 15 mg. The treatment may continue for 6 to 9 months or until breakthrough bleeding (spotting) stops.

Overdose:

If you take too much NORLUTATE you may experience:

- a depressed mood
- tiredness
- acne
- excessive hair growth on certain parts of your body

If you think you, or a person you are caring for, have taken too much NORLUTATE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you missed a dose, take it as soon as you remember. However, if it is almost time for your next dose, skip the missed dose and continue with your next scheduled dose. Do not double the dose to make up for a forgotten dose.

What are possible side effects from using NORLUTATE?

These are not all the possible side effects you may have when taking NORLUTATE. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Nausea or vomiting
- Stomach cramps, pressure, pain or bloating
- Lack of energy
- Changes in appetite and/or weight
- Changes in sex drive
- Pain in the leg
- Headaches or worsening of migraines
- Feeling dizzy
- Feeling nervous or irritable, mood swings

- Burning or painful urination
- Bladder infection
- Swollen or tender breasts
- Painful menstrual period
- Vaginal itching or discharge
- Genital pain during or after intercourse
- Absence of menstrual period
- Facial pigmentation
- Hair loss on the scalp or excessive hair growth on certain parts of your body
- Acne
- Breast milk drying up

The side effects listed above should disappear as your body adjusts to NORLUTATE. If they continue, become bothersome or severe, tell your healthcare professional.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Depression: persistent sad mood accompanied by difficulty in sleeping, weakness, lack of energy, fatigue		✓	
Hypothyroidism (underactive thyroid): **w**eight gain, tiredness, hair loss, muscle weakness, feeling cold, dry skin, constipation, puffy face, heavier than normal or irregular menstrual periods, enlarged thyroid gland		✓	
Unusual vaginal bleeding: irregular bleeding or spotting (unexpected bleeding that can happen between your normal menstrual periods), heavier or lighter menstrual flow, unusually long menstrual periods. Can be accompanied with lower abdomen pain, tenderness or swelling.		✓	
UNCOMMON			
Allergic Reaction: difficulty swallowing or breathing, wheezing, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue or throat			✓
Breast lumps		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Coronary thrombosis (blood clot inside a blood vessel of the heart): sudden pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the shoulder, chest, arm, or below the breastbone; discomfort radiating to the back, jaw, throat, arm, stomach, sweating, nausea, vomiting or dizziness; extreme weakness, anxiety, or shortness of breath, rapid or irregular heartbeats			✓
Deep vein thrombosis (blood clot in the legs) or **Thrombophlebitis** (inflammation of a vein often in the leg): sudden leg swelling or pain; redness, warmth, tenderness and pain in affected area			✓
Erythema multiforme (an allergic skin reaction): raised red or purple skin patches, possibly with blister or crust in the center; possibly swollen lips, mild itching or burning			✓
Eye problems: double or blurry vision, sudden complete or partial loss of vision in eye, bulging of the eyes, eye pain, migraine			✓
Gallstones: an attack often happens after a fatty meal. It may have intense pain in the upper abdomen, pain in right shoulder, results in nausea, and vomiting		✓	
Hyperglycemia (high blood sugar): increased thirst, frequent urination, dry skin, headache, blurred vision and fatigue		✓	
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitations		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Jaundice: yellowing of the skin or eyeballs, accompanied frequently by fever, fatigue, loss of appetite, dark-coloured urine, or light-coloured bowel movements			✓
Palpitation (fast-beating, fluttering or pounding heart): skipping beats, beating too fast, pounding, fluttering rapidly		✓	
Peripheral edema (swelling of the legs or hands caused by fluid retention): swollen or puffy legs or hands, feeling heavy, achy or stiff		✓	
Pulmonary embolism (blood clot in the lung): sharp pain in the chest, coughing blood, or sudden shortness of breath			✓
Stroke: sudden severe or worsening headache or vomiting, migraine, dizziness or fainting, disturbance of vision or speech, or weakness or numbness in an arm or leg, or numbness in the face			✓
Worsening of epilepsy in individuals with the condition			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store at room temperature (15°C - 30°C).
- Keep out of reach and sight of children.

If you want more information about NORLUTATE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.searchlightpharma.com, or by calling 1-855-331-0830.

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