CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

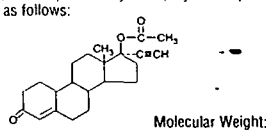
75951

DRAFT FINAL PRINTED LABELING

Rx only

WARNING:
THE USE OF NORETHINDRONE ACETATE DURING THE FIRST FOUR MONTHS OF PREGNANCY IS NOT RECOMMENDED.
Progestational agents have been used beginning with the first trimester of pregnancy in an attempt to prevent habitual abortion. There is no adequate evidence that such use is effective when such drugs are given during the first four months of pregnancy. Furthermore, in the vast majority of women, the cause of abortion is a defective ovum which progestational agents could not be expected to influence. In addition, the use of progestational agents, with their uterine-relaxant properties, in patients with fertilized defective ova may cause a delay in spontaneous abortion. Therefore, the use of such drugs during the first four months of pregnancy is not recommended.
Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias, 5 to 8 per 1,000 male births in the general population, may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risk to exposed female fetuses, but insofar as some of these drugs induce mild virilization of the external genitalia of the female fetus, and because of the increased association of hypospadias in the male fetus, it is prudent to avoid the use of these drugs during the first trimester of pregnancy.
If the patient is exposed to norethindrone acetate tablets, USP during the first four months of pregnancy or if she becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus.

DESCRIPTION:
Norethindrone acetate (17-hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one acetate), a synthetic, orally active progestin, is the acetic acid ester of norethindrone. It is a white, or creamy white, crystalline powder. The structural formula is as follows:



$C_{22}H_{28}O_3$ Molecular Weight: 340.47

Each tablet, for oral administration, contains norethindrone acetate 5 mg. In addition, each tablet contains the following inactive ingredients: anhydrous lactose, magnesium stearate, and microcrystalline cellulose.

CLINICAL PHARMACOLOGY:
Norethindrone acetate induces secretory changes in an estrogen-primed endometrium. It acts to inhibit the secretion of pituitary gonadotropins which, in turn, prevent follicular maturation and ovulation. On a weight basis, it is twice as potent as norethindrone.

INDICATIONS AND USAGE:
Norethindrone acetate tablets are indicated for the treatment of secondary amenorrhea, endometriosis, and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer.

CONTRAINDICATIONS:
Thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions.
Markedly impaired liver function or liver disease.
Known or suspected carcinoma of the breast.
Undiagnosed vaginal bleeding.
Missed abortion.
As a diagnostic test for pregnancy.

WARNINGS:
1. 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.
2. 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.
3. Masculinization of the female fetus has occurred when progestogens have been used in pregnant women.

PRECAUTIONS:
General:
1. The pretreatment physical examination should include special reference to breasts and pelvic organs, as well as a Papanicolaou smear.
2. Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunctions, require careful observation.
3. In cases of breakthrough bleeding, as in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.
4. Patients who have a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.
5. Any possible influence of prolonged progestogen therapy on pituitary, ovarian, adrenal, hepatic, or uterine functions awaits further study.
6. Data suggest that progestin therapy may have adverse effects on lipid and carbohydrate metabolism. The choice of progestin, its dose, and its regimen may be important in minimizing these adverse effects, but these issues will require further study before they are clarified. Women with hyperlipidemias and/or diabetes should be monitored closely during progestin therapy.
7. The age of the patient constitutes no absolute limiting factor, although treatment with progestogens may mask the onset of the climacteric.
8. The pathologist should be advised of progestogen therapy when relevant specimens are submitted.

Information for the Patient:
See text which appears at the end of this insert.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:
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. There is no general agreement as to whether the nodules are benign or malignant. Their significance with respect to humans has not been established.

Pregnancy Category X:
See Boxed Warning.

Nursing Mothers:
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.

Pediatric Use:
Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS:
The following adverse reactions have been observed in women taking progestins:
Breakthrough bleeding.
Spotting.
Change in menstrual flow.
Amenorrhea.

NORETHINDRONE ACETATE TABLETS, USP

(Five Patient Information Leaflets Enclosed - Tear at Perforation)

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Edema.
Changes in weight (decreases, increases).
Changes in cervical erosion and cervical secretions.
Cholestatic jaundice.
Rash (allergic) with and without pruritus.
Melasma or chloasma.
Mental depression.
Progestins may alter the result of pregnanediol determinations. The following laboratory results may be altered by the concomitant use of estrogens with progestins:
Hepatic function.
Coagulation tests - increase in prothrombin, factors VII, VIII, IX, and X.
Increase in PBI, BEI, and a decrease in T^3 uptake.
Reduced response to metyrapone test.
A statistically significant association has been demonstrated between use of estrogen-progestogen combination drugs and the following serious adverse reactions: thrombophlebitis, pulmonary embolism, and cerebral thrombosis and embolism. For this reason, patients on progestogen therapy should be carefully observed. Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: Neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.
The following adverse reactions have been observed in patients receiving estrogen-progestogen combination drugs:
1. Rise in blood pressure in susceptible individuals.
2. Premenstrual-like syndrome.
3. Changes in libido.
4. Changes in appetite.
5. Cystitis-like syndrome.
6. Headache.
7. Nervousness.
8. Dizziness.
9. Fatigue.
10. Backache.
11. Hirsutism.
12. Loss of scalp hair.
13. Erythema multiforme.
14. Erythema nodosum.
15. Hemorrhagic eruption.
16. Itching.

In view of these observations, patients on progestogen therapy should be carefully observed.

DOSAGE AND ADMINISTRATION:

Therapy with norethindrone acetate must be adapted to the specific indications and therapeutic response of the individual patient. This dosage schedule assumes the interval between menses to be 28 days. Secondary amenorrhea, abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology: 2.5 to 10 mg norethindrone acetate may be given daily for 5 to 10 days during the second half of the theoretical menstrual cycle to produce an optimum secretory transformation of an endometrium that has been adequately primed with either endogenous or exogenous estrogen.
Progestin withdrawal bleeding usually occurs within three to seven days after discontinuing norethindrone acetate therapy. Patients with a past history of recurrent episodes of abnormal uterine bleeding may benefit from planned menstrual cycling with norethindrone acetate.
Endometriosis: Initial daily dosage of 5 mg norethindrone acetate for two weeks. Dosage should be increased by 2.5 mg per day every two weeks until 15 mg per day of norethindrone acetate is reached. Therapy may be held at this level for six to nine months or until annoying breakthrough bleeding demands temporary termination.

HOW SUPPLIED:

Norethindrone Acetate Tablets, USP are available as:

5 mg: White, oval, flat-faced, beveled-edge, scored tablet. Debossed with b on one side and **211/5** on the scored side.
Available in bottles of:
50 NDC 0555-0211-10

Dispense in a well-closed container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).

INFORMATION FOR THE PATIENT

Your doctor has prescribed norethindrone acetate tablets, USP, a progestin, for you. Norethindrone acetate is similar to the progesterone hormones naturally produced by the body. Progestins are used to treat menstrual disorders and to test if the body is producing certain hormones.

Warning:

Progesterone or progesterone-like drugs have been used to prevent miscarriage in the first few months of pregnancy. No adequate evidence is available to show that they are effective for this purpose. Furthermore, most cases of early miscarriage are due to causes which could not be helped by these drugs.
There is an increased risk of minor birth defects in children whose mothers take this drug during the first four months of pregnancy. Several reports suggest an association between mothers who take these drugs in the first trimester of pregnancy and genital abnormalities in male and female babies.
The risk to the male baby is the possibility of being born with a condition in which the opening of the penis is on the underside rather than the tip of the penis (hypospadias). Hypospadias occurs in about 5 to 8 per 1,000 male births and is about doubled with exposure to these drugs. There is not enough information to quantify the risk to exposed female fetuses, but enlargement of the clitoris and fusion of the labia may occur, although rarely.
Therefore, since drugs of this type may induce mild masculinization of the external genitalia of the female fetus, as well as hypospadias in the male fetus, it is wise to avoid using the drug during the first trimester of pregnancy.
These drugs have been used as a test for pregnancy but such use is no longer considered safe because of possible damage to a developing baby. Also, more rapid methods for testing for pregnancy are now available.
If you take norethindrone acetate tablets, USP and later find you were pregnant when you took it, be sure to discuss this with your doctor as soon as possible.

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POMONA, NY 10970

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