Estracon®

(Conjugated Estrogen USP 0.625mg)

Presentation: Each white Extended-Release **Estracon®** tablet contains Conjugated Estrogens USP 0.625mg.

Description: Estracon® (conjugated estrogens) for oral administration is a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains the sodium salts of water-soluble sulfate esters of estrone, equilin, and 17 alpha-dihydroequilin, together with smaller amounts of 17 alpha-estradiol, equilenin, 17 alpha-dihydroequilenin, 17 beta-dihydroequilin, 17 beta-dihydroequilenin, 17 beta-estradiol, and delta 8,9-dehydroestrone.

Clinical Pharmacology: Estrogens are important in the development and maintenance of the female urogenital system and secondary sex characteristics. They promote growth and development of the vagina, uterus, and fallopian tubes, and enlargement of the breasts. Indirectly, they contribute to the shaping of the skeleton, maintenance of tone and elasticity of urogenital structures, changes in the epiphyses of the long bones associated with the pubertal growth spurt and its termination, growth of axillary and pubic hair, and pigmentation of the nipples and genital tissues. Decline of ovarian estrogenic and progestogenic activity at the end of the menstrual cycle can result in menstruation, although the cessation of progesterone secretion is the most important factor in the mature ovulatory cycle. However, in the preovulatory or anovulatory cycle, estrogen is the primary determinant in the onset menstruation. Eestrogen also affects the release of pituitary gonadotropins. The pharmacologic effects of conjugated estrogens are similar to those of endogenous estrogens. In responsive tissues (female urogenital organs, breasts, hypothalamus, pituitary) estrogens enter the cell and are transported into the nucleus. As a result of estrogenic activity, specific RNA and protein synthesis occurs. Oral administration of **Estracon®** to postmenopausal women increases serum high density lipoprotein cholesterol (HDL-C) levels and decreases low density lipoprotein cholesterol (LDL-C) levels. This improves the lipid profile and is recognized as a factor responsible for the beneficial effects of **Estracon®** on the risk of coronary heart disease in postmenopausal women. Conjugated Estrogens are soluble in water and are well absorbed from the gastrointestinal tract. Metabolism and inactivation occur primarily in the liver. Some estrogens are excreted in bile; however, they are reabsorbed from the intestine and returned to the liver through the portal venous system. Water-soluble estrogen conjugates are strongly acidic and are ionized in body fluids, which favors excretion through the kidneys since tubular reabsorption is minimal.

Clinical Efficacy:

Vasomotor symptoms associated with estrogen deficiency

Hot flushes, (feelings of intense heat over the upper trunk and face, with flushing of the skin and sweating) occur in 80% of the postmenopausal women as a result of the decrease in ovarian hormones. These vasomotor symptoms are seen in women whether menopause is surgically induced or spontaneous. However, hot flushes may be more severe in women who undergo surgical menopause. Hot flushes can begin before the cessation of menses. Double-blind, randomized, placebo-controlled crossover studies have confirmed a significant reduction in hot flushes experience by menopausal women taking **Estracon®**.

Osteoporosis associated with estrogen deficiency

Estrogen replacement therapy is the most effective single modality for the prevention of osteoporosis (loss of bone mass) in postmenopausal women. Estrogen reduces bone resorption and retards or halts postmenopausal bone loss. Case-control studies have shown up to 60 percent reduction in hip and writs fractures in women whose estrogen replacement was begun within a few years of menopause. Studies also suggest that estrogen reduces the rate of vertebral fractures. One clinical study demonstrated that even when estrogen was started as late as fifteen years after menopause, further loss of bone mass was prevented but no restoration of bone mass was observed. The effect on bone mass conservation is sustained only as long as conjugated estrogen therapy is continued. Different ethnic groups are at different risk for osteoporosis.

Cardiovascular Benefit

Case-control, cohort and coronary angiography studies have been conducted investigating the association between postmenopausal oral estrogen therapy and cardiovascular disease. The majority of studies show a decreased risk of coronary heart disease in postmenopausal women taking estrogen replacement therapy. An analysis of the available data shows an overall decrease in the risk of coronary heart disease of approximately 50% in women treated with conjugated estrogen. In the majority of these studies conjugated estrogens were the predominant therapy. This beneficial effect appears to be related to several mechanisms of action including, but perhaps not limited to, beneficial effects on lipids and lipoproteins and direct effects on the coronary vessels. Although it has been reported that progestogen therapy may attenuate the beneficial effects of estrogen on lipids, the overall effect on coronary heart disease is unknown. Conjugated Estrogen should be used with other important measures such as dietary changes, exercise, and cessation of smoking to achieve optimal cardiovascular benefit.

Atrophic vaginitis and atrophic urethritis associated with estrogen deficiency

In the absence of estrogen stimulation, the vulvar and vaginal tissues shrink, the vaginal walls become thin and dry, and rugal folds disappear. Tenderness and pruritus, with resulting dysuria and dyspareunia, may occur. Fissures and ulcerations of tissue with spotting or bleeding may result from coitus. These changes are reversible with the administration of estrogen replacement therapy.

Female Hypoestrogenism

Estrogen replacement therapy is indicated in hypoestrogenism related to female hypogonadism or primary ovarian failure. Primary ovarian failure starting early in life will lead to delayed closure of the epiphyses and retarded bone maturation. Long term estrogen deficiency in any age group will usually lead to osteoporosis (for efficacy with estrogen replacement therapy see osteoporosis). Estrogen therapy is associated with the appearance of female characteristics in these patients.

Indications (see Clinical Efficacy)

1. Moderate-to-severe vasomotor symptoms associated with estrogen deficiency.
2. Prevention and management of osteoporosis associated with estrogen deficiency.
3. Decrease of the risk of coronary heart disease and its associated mortality in postmenopausal women.
4. Atrophic vaginitis and atrophic arthritis.
5. Female hypoestrogenism.

Contraindications:

1. Known or suspected cancer of the breast.
2. Known or suspected estrogen-dependent neoplasia.
3. Known or suspected pregnancy.
4. Undiagnosed abnormal genital bleeding.
5. Active thrombophlebitis or thromboembolic disorders.
6. Hypersensitivity to any of the components of **Estracon®** Tablets.

Warnings: Estrogen therapy without the addition of a progestogen in women with a uterus has been reported to increase the risk of endometrial hyperplasia/carcinoma. The risk appears to depend on both duration of treatment and estrogen dose. The patient should be reassessed at least on an annual basis. Studies have indicated a reduced risk of endometrial cancer when a progestogen is administered with estrogen replacement therapy. There are possible additional risks which may be associated with the inclusion of a progestogen in hormone replacement therapy regimens. These include adverse effects on carbohydrate and lipid metabolism. The choice of progestogen may be important in minimizing these risks. An increased risk of gallbladder disease in women receiving postmenopausal estrogen has been reported. Some studies have suggested a possible increased incidence of breast cancer in those women on estrogen therapy taking higher doses for prolonged periods of time. The majority of studies, however, have not shown an association with the usual doses used for estrogen replacement therapy. Women on this therapy should have regular breast examinations and should be instructed in breast self-examination. Doses of **Estracon®** used should not exceed the recommended doses.

Use during pregnancy-estrogen should not be used during pregnancy

Estrogen therapy during pregnancy is associated with an increased risk of congenital defects in the reproductive organs of the male and female fetus, an increased risk of vaginal adenosis, squamous-cell dysplasia of the cervix, and vaginal cancer in the female later in life. There is no indication for estrogen therapy during pregnancy. Estrogens are effective in the prevention or treatment of threatened or habitual abortion.

Precautions: A complete medical and family history should be obtained prior to the initiation of any estrogen therapy. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolaou smear. Patients with a uterus should be monitored at least annually for signs of endometrial hyperplasia or endometrial cancer. When concurrent progestogen therapy is used in women with a uterus, monitoring should include endometrial sampling. Certain patients may develop undesirable manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. In the event of abnormal vaginal bleeding, adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy. Where no pathologic cause is found for abnormal vaginal bleeding, dose reduction of cycling may be indicated. Pre-existing uterine leiomyomata may increase in size during estrogen use. Women on estrogen replacement therapy have not been reported to have an increased risk of thrombophlebitis and/or thromboembolic disease. However, there is insufficient information regarding women who have a history of thromboembolic disease to determine risk. There is no adequate evidence that estrogens are effective for nervous symptoms or depression which may occur during menopause and they should not be used to treat such conditions. If feasible, estrogen should be discontinued at least four weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Because estrogens may cause some degree of fluid retention, conditions which might be influenced by this factor such as asthma, epilepsy, migraine and cardiac or renal dysfunction require careful observation. Estrogen may be poorly metabolized in patients with impaired liver function and they should be administered with caution in such patients. Estrogen should be used with caution in patients with metabolic bone diseases associated with hypercalcemia. Patients should be advised that the resumption of menses associated with estrogen replacement therapy in postmenopausal women is not indicative of fertility. Estracon® is not a contraceptive. Women of child bearing potential desiring contraception should be advised to adhere to non-hormonal contraceptive methods.

Mutagenesis and Carcinogenesis – Long-term continuous administration of natural and synthetic estrogen in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver.

Use during Lactation – As a general principle the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

Adverse Reactions: The most serious adverse reactions associated with the use of estrogen are indicated under Warnings and Precautions. The following additional adverse reactions have been reported with estrogenic therapy.

Genitourinary System: Breakthrough bleeding, spotting, change in menstrual flow, amenorrhea.

Breasts: Tenderness, enlargement, secretion.

Gastrointestinal: Nausea, vomiting, abdominal cramps, bloating, cholestatic jaundice.

Skin: Chloasma or melasma which may persist when drug is discontinued, alopecia, rash.

Eyes: Steepening of the corneal curvature; intolerance to contact lenses.

Central Nervous System: Headache, migraine, dizziness; chorea.

Miscellaneous: Increase or decrease in wiehgt; edema; changes in libido, aggravation of porphyria.

Drug Interactions: Rifampin reportedly decreases estrogenic activity during concomitant use with estrogen. This effect has been attributed to enhanced metabolism of estrogen, presumably by induction of hepatic microsomal enzymes.

Dosage and Administration: Administration of **Estracon®** may be continuous (e.g., without a break in therapy) or cyclic (e.g., three weeks on and one week off.) The lowest effective dose should be administered. **Estracon®** can be used concomitantly with progestogen.

Use: The addition of a progestogen during estrogen administration reduces the risk of endometrial hyperplasia and endometrial carcinoma, which have been associated with the use of unoposed estrogen. Morphological and biochemical studies of the endometrium suggest that an adequate dose of progestogen for at least 10-14 days per cycle will significantly reduce hyperplastic changes. Since progestogens are administered to reduce the risk of hyperplastic hanges of the endometrium, patients without a uterus do not require a progestogen for this purpose.

Usual dosage range:

OSTEOPOROSIS: 0.625mg daily. This dose is required for bone mass conservation.

CARDIOVASCULAR BENEFIT : 0.625mg – 1.25mg daily.

FEMALE HYPOESTROGENISM : 0.3mg – 1.25mg daily. Doses are adjusted depending on the severity of symptoms and responsiveness of the endometrium. Dose should be individualized to achieve optimum patient response.

Over dosage: Numerous reports of ingestion of large doses of estrogen-containing oral contraceptives by young children indicate that acute serious ill effects have not been observed. Overdosage of estrogens may cause nausea, and withdrawal bleeding may occur in females.

Commercial Supply: Box containing 28 tablets in glass bottle.

Storage conditions: Store in a cool and dry place, protected from light and moisture, temperature below 25^{o}c (77^{o} F).

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Manufactured by :

RENATA LIMITED

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Issue date: March, 2010