PRODUCT MONOGRAPH

NEO-ESTRONE

ESTERIFIED ESTROGEN

TABLETS

1.25mg, 0.625mg, 0.3mg

ESTROGEN

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PHARMACOLOGIC CLASSIFICATION

ESTROGEN

Warning

As the Women's Health Initiative (WHI) study results indicated increased risk of myocardial infarction (MI),stroke, invasive breast cancer , pulmonary emboli, and deep venous thrombosis in postmenopausal women receiving treatment with combined conjugated equine estrogens and medroxyprogesterone acetate compared to those receiving placebo tablets, the following should be highly considered:

. Estrogens with or without progestins **should not** be prescribed for primary or secondary prevention of cardiovascular diseases.
. Estrogens with or without progestins should be prescribed at **the lowest effective dose** for the approved indication.
. Estrogens with or without progestins should be prescribed for **the shortest period** possible for the recognized indication.

ACTIONS AND CLINICAL PHARMACOLOGY

NEO-ESTRONE TABLETS contain a sulphate ester form of estrone used in relieving the menopausal and post-menopausal symptoms of naturally or surgically induced estrogen deficiency states.
In general, estrogens are of importance in the development and maintenance of the female reproductive system as well as secondary sexual characteristics. After menopause the ovarian follicle produces less and less estradiol to convert to estrone. Whereas the ratio of circulating estradiol to estrone was close to equal before menopause, after menopause most of the endogenous circulating hormone is the sulphate ester form of estrone coming from the conversion of androstendione secreted by the adrenal cortex. Metabolic conversion occurring mostly in the liver creates an equilibrium of various forms of estrogen through interconversions. Sulfated forms of estrone create a reservoir for deriving more active forms of estrogen such as estradiol and estrone. Estrogens circulate in the blood stream usually bound to SHBG (sex hormone bound globulin) or to albumin. Unbound estrogen enters targeted cells to bind to an estrogen receptor and then by activating adjacent genes causes the apparition of the various attributed effects of the female hormones.

CLINICAL PHARMACOLOGY OF ESTROGEN
There have been no dose ranging studies specific to NEO-ESTRONE TABLETS for the purpose of establishing the recommended dose for the approved indication.

PHARMACOKINETICS OF NEO-ESTRONE TABLETS
NEO-ESTRONE TABLETS consist in a blend of sodium salts of the 3-sulfate esters of: estrone, equilin, equilenin, 17 alpha-dihydroequilin and 17 alpha-dihydroequilenin. However, estrone and equilin dominate the composition with 81% and 13% respectively and are the primary source of estrogen available for absorption. Administered hormone is metabolised by the body much the same as endogenous hormone. Ingested hormones, sodium estrone sulphate and sodium equilin sulphate are metabolized mostly by the liver to be converted to non-esterified forms. Complex metabolic processes create a dynamic equilibrium of interconversion between estrone and estradiol and between esterified and non esterified forms. A portion of the estrogen is excreted into the bile to be reabsorbed via the intestine and back to the liver. During the course of enterohepatic recirculation, estrogens are desulfated and resulfated, undergo degradation through conversion to less active estrogens such as estriol, are oxidized to nonestrogenic substances which interact with catecholamine metabolism and are conjugated with glucuronic acids to be excreted in the urine.

PIVOTAL CLINICAL TRIALS
There have been no pivotal clinical trials specific to NEO-ESTRONE TABLETS.

INDICATIONS AND CLINICAL USE

NEO-ESTRONE TABLETS are prescribed in the treatment of menopausal and post menopausal symptoms including vulvar and vaginal atrophy.

NEO-ESTRONE TABLETS should be prescribed with an appropriate dosage of a progestin for women with intact uteri to prevent endometrial hyperplasia/carcinoma.

CONTRAINDICATIONS:

Estrogens used either alone or with a progestin are contraindicated in patients with any of the following disorders:

. Active or past history of arterial thromboembolic disease (eg. stroke, myocardial infarction, coronary heart disease).

. Classical migraine.

. Personal history of known or suspected estrogen/progestin dependent neoplasia such as breast or endrometrial cancer.

. Endometrial hyperplasia.

. Undiagnosed abnormal genital bleeding.

. Known or suspected pregnancy.

. Active or past history of confirmed venous thromboembolism (such as deep venous thrombosis or pulmonary embolism) or active thrombophlebitis.

. Active thrombophlebitis, thrombosis, or thromboembolic disorders, or a history of these conditions.

. Partial or complete loss of vision due to ophthalmic vascular disease.

. Known or suspected hypersensitivity to any component of the product.

. Active hepatic dysfunction or disease, especially of the obstructive type.

WARNINGS:

See the **boxed warnings** at the front page**.**

CARDIOVASCULAR DISORDERS
Available epidemiological data indicate that the use of estrogen with or without progestin is associated with an increased risk of stroke, and coronary heart disease. WHI-trial's results concluded that there are more risks than benefits among women using combined Hormone Replacement Therapy (HRT), compared to the group using placebo. In 10,000 women on combined HRT (conjugated equine estrogens/medroxyprogesterone acetate) over one year period , there were seven more cases of coronary heart disease (37 on combined HRT versus 30 on placebo) and eight more cases of strokes (29 vs 21).[1]

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 2.5mg 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.[2] From the original HERS trial, 2321 women consented to participate in an open label extension of HERS, 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.[3]

BREAST CANCER

Current epidemiological data indicate that the use of combined HRT is associated with an increased risk of invasive breast cancer. WHI-trial's results concluded that there are more risks than benefits among women using combined HRT (conjugated equine estrogens/medroxyprogesterone acetate) compared to the group using placebo. In 10,000 women on combined HRT over one year period, there were eight more cases of invasive breast cancer (38 on combined HRT versus 30 on placebo).[1]

The WHI study reported that the invasive breast cancers diagnosed in the estrogen plus progestin group were similar in histology but were larger (mean [SD],1.7cm [1.1] vs 1.5 cm [0.9], respectively; P=0.04) and were at a more advanced stage compared with those diagnosed in the placebo group.

The WHI trial also reported that the percentage of women with abnormal mammograms (recommendations for short-interval follow-up, a suspicious abnormality, or highly suggestive of malignancy) was significantly higher in the estrogen plus progestin group versus the placebo group. This difference appeared at year one and persisted in each year thereafter.[4]

It is recommended that estrogens not be given to women with existing breast cancer or those with a previous history of the disease. There is a need for caution in prescribing estrogens for women with known risk factors associated with the development of breast cancer such as strong family history of breast cancer (first degree relative) or who present a breast condition with an increased risk (abnormal mammograms and\or atypical hyperplasia at breast biopsy). 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 be evaluated.

It is recommended that women undergo mammography prior to the start of HRT treatment and at regular intervals during treatment, as deemed appropriate by the treating physician and according to the perceived risks for each patient.

The overall benefits and possible risks of hormone replacement therapy should be fully considered and discussed with patients. It is important that the modest increased risk of being diagnosed with breast cancer after 4 years of treatment with HRT(as reported in the results of the WHI-trial) be discussed with the patient and weighed against its known benefits.

Instructions for regular self-examination of the breasts should be included in this counselling.

VENOUS THROMBOEMBOLISM

Recent epidemiological data indicate that use of estrogen with or without progestin is associated with an increased risk of developing venous thromboembolism (VTE). WHI-trial's results concluded that there are more risks than benefits among women using combined HRT(conjugated equine estrogens/medroxyprogesterone acetate), compared to the group using placebo. In 10,000 women on combined HRT over a period of one year, there were eighteen more cases of total blood clots in the lungs and legs (34 on combined HRT versus 16 on placebo).[1]

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) and severe obesity (body mass index> 30Kg/m2). The risk of VTE also increases with age and smoking.

The risk of VTE may be temporarily increased with prolonged immobilization, major elective surgery or post traumatic surgery, or major trauma (if feasible, estrogens should be discontinued at least 4 weeks before major surgery which may be associated with an increased risk of thromboembolism, or during periods of prolonged immobilization).

In women on HRT, attention should be given to prophylactic measures to prevent VTE following surgery. Also, patients with varicose veins should be closely supervised. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, hormone therapy should be discontinued immediately.

ENDOMETRIAL HYPERPLASIA & ENDOMETRIAL CARCINOMA
The use of unopposed estrogen in women with intact uteri increases the risk of endometrial hyperplasia, which may increase the risk of endometrial cancer. The addition of a progestin to estrogen replacement therapy in women with intact uteri reduces the risk of endometrial hyperplasia (see Dosage and Administration).

GALLBLADDER DISEASES
A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving postmenopausal estrogens has been reported.

DEMENTIA
Current epidemiological evidence indicates that the use of combined HRT is associated with a significantly increased risk of developing probable dementia. The Women's Health Initiative Memory Study, a clinical substudy of the WHI, followed 4532 post-menopausal women age 65 and over and free of dementia at baseline. There was a reported two-fold increase in the relative risk of developing probable dementia after an average follow-up of 4.05 years in the group treated with daily 0.625mg conjugated equine estrogen plus 2.5 mg medroxprogesterone versus those treated with placebo (hazard ratio [HR] 2.05, 95% confidence interval [CI], 1.21-3.48). This increased risk would result in an additional 23 cases of dementia per 10 000 women per year (45 vs 22 per 10 000 person-years;P=.01).[5]

PRECAUTIONS

- Before NEO-ESTRONE TABLETS are administered, the patient should have a complete physical exam 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 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 and should include at least those procedures outlined above.
  It is important that patients are encouraged to practice frequent self-examination of the breasts.

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

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

- Symptoms and physical findings associated with a previous diagnosis of endometriosis may reappear or become aggravated with estrogen use.

- Caution is advised in patients with a history of estrogen related jaundice and pruritus. If cholestatic jaundice develops during the treatment, the treatment should be discontinued and appropriate investigations carried out.

- Patients who develop visual disturbances, classical migrane, transient aphasia, paralysis, or loss of consciousness should discontinue medication.

- If feasible, estrogens should be discontinued 4 weeks before major surgery which may be associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

- Women using hormonal replacement therapy (HRT) sometimes experience increased blood pressure. Blood pressure should be monitored with HRT use. Elevation of blood pressure in previously normotensive or hypertensive patients should be investigated and HRT therapy may have to be discontinued.

- Estrogens may cause fluid retention. Therefore, particular caution is indicated in cardiac or renal dysfunction, epilepsy or asthma. Treatment should be stopped if there is a increase in epileptic seizures. 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.

- Because the prolonged use of estrogens influences the metabolism of calcium and phosphorus, estrogens should be used with caution in patients with metabolic and malignant bone diseases associated with hypercalcemia and in patients with renal insufficiency.

- A worsening of glucose tolerance and lipid metabolism have been observed in a 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.

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

- 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 the section under **Laboratory Tests**.

Drug Interactions

Estrogens may diminish the effectiveness of anticoagulant, antidiabetic and antihypertensive agents.

Preparations inducing liver enzymes (e.g , barbiturates, hydantoins, carbamazepine, meprobamates, phenylbutazone or rifampicin) may interfere with the activity of orally administered estrogens.

The following section contains information on drug interactions with ethinyl estradiol containing products (specifically, oral contraceptives) that have been reported in the public literature. It is unknown whether such interactions occur with drug products containing other types of estrogens.

The metabolism of ethinyl estradiol is increased by rifampin and anticonvulsants such as phenobarbital, phenytoin and carbamazepine. Coadministration of troglitazone and certain ethinyl estradiol containing drug products (e.g., oral contraceptives containing ethinyl estradiol) reduce the plasma concentrations of ethinyl estradiol by 30 percent.

Ascorbic acid and acetaminophen may increase AUC and/or plasma concentrations of ethinyl estradiol. Coadministration of atorvastatin and certain ethinyl estradiol containing drug products (e.g., oral contraceptives containing ethinyl estradiol) increase AUC values for ethinyl estradiol by 20 percent.

Clinical pharmacokinetic studies have not demonstrated any consistent effect of antibiotics (other than rifampin) on plasma concentrations of synthetic steroids.

Drug products containing ethinyl estradiol may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporine, prednisolone, and theophylline have been reported with concomitant administration of certain drugs containing ethinyl estradiol (e.g., oral contraceptives containing ethinyl estradiol). In addition, these drugs containing ethinyl estradiol may induce the conjugation of other compounds.

Decreased plasma concentrations of acetaminophen and increased clearance of temazepam, salicyclic acid , morphine and clofibric acid have been noted when these drugs were administered with certain ethinyl estradiol containing drug products (e.g., oral contraceptives containing ethinyl estradiol).

Concomitant administration of aminoglutethimide with medroxyprogesterone acetate (MPA), may significantly reduce the bioavailability of MPA.

It was found that some herbal products (e.g. St. John's wort) which are available as OTC products might affect metabolism, and therefore, efficacy and safety of estrogen / progestin products.

Physicians and other health care providers should be aware of other non-prescription products concomitantly used by the patient, including herbal and natural products, obtained from the widely spread health stores.

Laboratory Tests

The results of certain endocrine and liver function tests may be affected by estrogen containing products.

- increased sulfobromophthalein retention;
- 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.
- increased thyroxine-binding globulin (TBG), leading to increased circulating total thyroid hormone (T4) as measured by column or radioimmunoassay; free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered;
- 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.
- reduced response to the METOPIRONE test;
- impaired glucose tolerance
- reduced serum folate concentration;
- increased serum triglycerides and phospholipids concentration;

NEO-ESTRONE TABLETS have not been subjected to clinical trials and therefore it has not been reported that this specific product had any effect on fibrinogen, antithrombin III, TBG, CBG, SHBG, proteinC system (protein C/S), activated protein C resistance(APC resistance) due to factor V Leiden mutation. However, the potential for occurrence does exist for estrogen products.

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 HRT therapy when relevant specimens are submitted.

ADVERSE REACTIONS

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

NEO-ESTRONE TABLETS have not been subjected to clinical trials and therefore the incidence of adverse effects specific to this product cannot be expressed as a percentage.

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

. Gastrointestinal

Nausea; vomiting; abdominal discomfort (cramps, pressure, pain); bloating; gallbladder disorder; asymptomatic impaired liver function; cholestatic jaundice.

. Genitourinary

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

. Skin

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

. Endocrine

Breast swelling and tenderness; increased blood sugar levels; decreased glucose tolerance; sodium retention.

. Cardiovascular/Hematologic

Palpitations; isolated cases of thrombophlebitis; thromboembolic disorders;
Exacerbations of varicose veins; increase in blood pressure **(see Warnings and Precautions)**. Coronary thrombosis; altered coagulation tests **(see Laboratory Tests under Precautions)**.

. Central Nervous System

Aggravation of migraine episodes; headaches; mental depression; nervousness; dizziness; fatigue; irritability; neuro-ocular lesions (e.g. retinal thrombosis, optic neuritis).

. Ophthalmic

Visual disturbances; steepening of the corneal curvature; intolerance to contact lenses; neuro-ocular lesions **(see CNS above)**.

. Miscellaneous

Changes in appetite; changes in body weight; edema; neuritis; change in libido; musculoskeletal pain including leg pain not related to thromboembolic disease (usually transient, lasting 3-6 weeks) may occur.

If adverse symptoms persist, the prescription of HRT should be re-considered.

SYMPTOMS AND TREATMENT OF OVER DOSAGE

Symptoms

Numerous reports of ingestion of large doses of estrogen products and estrogen-containing oral contraceptives by young children have not revealed acute serious ill effects. Overdosage with estrogen may cause nausea, breast discomfort, fluid retention, bloating or vaginal bleeding in women.

Treatment

In case of overdosage, ingested drug should be removed by gastric lavage.

Symptomatic treatment should be given.

DOSAGE AND ADMINISTRATION

Esterified estrogens are usually prescribed in a cyclical regimen of 25 days on drug followed by 5 days off or in a continuous uninterrupted therapy based on the individual's requirements. In women with an intact uterus, a progestin should be coadministered for at least 10 days, preferably 12 to 14 days, of each cycle to reduce the risk of overstimulation of the endometrium and development of endometrial hyperplasia. In patients without a uterus a progestin is not required. The usual dosage range is 0.3 to 1.25mg daily. Adjust the dosage upward or downward according to the severity of the symptoms and response of the patient. For maintenance adjust the dosage downward to the lowest level that provides effective control.

PHARMACEUTICAL INFORMATION

NEO-ESTRONE TABLETS:
Contain: contain an estrogenic mixture comprised primarily of sodium estrone sulphate and sodium equiline sulphate and in either of the following strengths: 1.25 or 0.625 or 0.3 mg per tablet

Non-medicinal ingredients common to NEO-ESTRONE 1.25 NEO-ESTRONE 0.625 and NEO-ESTRONE 0.3 Tablets: starch, lactose, calcium carbonate, sodium carboxymethylcellulose, tribasic calcium phosphate, talc, magnesium stearate, mu-crystalline cellulose.

Non-medicinal solids contained in the tablet coating:

NEO-ESTRONE 1.25 (pink coloured tablet)coating solids: sucrose, erythrosine lake, titanium dioxide, povidone, FD&C Blue #2, sodium benzoate.

NEO-ESTRONE 0.625(green coloured tablet)coating solids: sucrose, titanium dioxide, FD&C Blue #1, FD&C Yellow #5, povidone, sodium benzoate.

NEO-ESTRONE 0.3 (yellow coloured tablet) coating solids: sucrose, FD&C Yellow #5, titanium dioxide, sodium benzoate.

STORAGE

NEO-ESTRONE TABLETS can be stored at room temperature (15 to 30 degrees Centigrade).

REFERENCES

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