

# ESTRACE®

## 17β estradiol Estrogen

**INDICATIONS AND CLINICAL USE** ESTRACE® (17β-estradiol Tablets) tablets are indicated for:

- the symptomatic relief of menopausal symptoms.
- ESTRACE® may also contribute to the prevention of osteoporosis in naturally occurring or surgically induced estrogen-deficiency states when combined with other important therapeutics such as diet, calcium and vitamin D intake, smoking cessation and regular physical weight bearing exercises.

The use of ESTRACE® in the prevention of osteoporosis is to be continued in light of other available therapies.

In patients with an intact uterus, ESTRACE® should always be supplemented by sequential administration of a progestogen in order to prevent endometrial hyperplasia or carcinoma.

### CONTRAINDICATIONS

Estrogen including ESTRACE® should not be administered to patients with any of the following conditions:

- Active hepatic dysfunction or disease, especially of the obstructive type.
- Personal history of known or suspected estrogen-dependent malignant neoplasia (e.g. breast cancer or endometrial cancer).
- Endometrial hyperplasia.
- Known or suspected pregnancy.
- Undiagnosed abnormal genital bleeding.
- Active or past history of arterial thromboembolic disease (eg. stroke, myocardial infarction, coronary heart disease).
- Classical migraine
- Active or past history of confirmed venous thromboembolism (such as deep vein thrombosis or pulmonary embolism) or active thrombophlebitis.
- Partial or complete loss of vision or diplopia, from ophthalmic vascular disease.
- Lactation.
- Hypersensitivity to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the Product Monograph.

### WARNINGS AND PRECAUTIONS

#### Serious Warnings and Precautions

The Women's Health Initiative (WHI) trial examined the health benefits and risks of combined *estrogen plus progestin* therapy (n=16,608) and *estrogen-alone* therapy (n=10,739) in postmenopausal women aged 50 to 79 years.

The *estrogen plus progestin* arm of the WHI trial indicated increased risk of myocardial infarction (MI), stroke, invasive breast cancer, pulmonary emboli and deep vein thrombosis in postmenopausal women receiving treatment with combined conjugated equine estrogens (CEE, 0.625 mg/day) and medroxyprogesterone acetate (MPA, 2.5 mg/day) for 5.2 years compared to those receiving placebo.

The *estrogen-alone* arm of the WHI trial indicated an increased risk of *stroke* and *deep vein thrombosis* in hysterectomized women treated with CEE-alone (0.625 mg/day) for 6.8 years compared to those receiving placebo. Therefore, the following should be given serious consideration at the time of prescribing:

1. Estrogens with or without progestins **should not** be prescribed for primary or secondary prevention of cardiovascular diseases.
2. Estrogens with or without progestins should be prescribed at the **lowest effective dose** for the approved indication.
3. Estrogens with or without progestins should be prescribed for the **shortest period** possible for the approved indication.
4. The use of ESTRACE® for the prevention of osteoporosis should be considered in light of other available therapies.

#### WARNINGS SEE BOXED WARNINGS.

#### Carcinogenesis and Mutagenesis

##### Breast cancer

Available epidemiological data indicate that the use of combined estrogen plus progestin by postmenopausal women is associated with an increased risk of invasive breast cancer. In the estrogen plus progestin arm of the WHI trial, among 10,000 women over a one-year period, there were:

- 8 more cases of invasive breast cancer (38 on combined HRT versus 30 on placebo)

The WHI study also reported that the invasive breast cancers diagnosed in the *estrogen plus progestin* group were similar in histology but were larger (mean [SD], 1.7 cm [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 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. In the *estrogen-alone* arm of the WHI trial, there was no statistically significant difference in the rate of invasive breast cancer

in hysterectomized women treated with conjugated equine estrogens versus women treated with placebo.

In a pivotal clinical study with ESTRACE® (n=64) on the prevention of early post-menopausal bone loss (see **CLINICAL TRIALS** Section in Product Monograph), three (3) abnormal mammograms were reported post-treatment, however, none showed evidence of malignancy.

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 also 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 combined estrogen plus progestin HRT (as reported in the results of 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 counseling.

#### Endometrial hyperplasia & endometrial carcinoma

The use of unopposed estrogen by women with intact uteri increases the risk of endometrial hyperplasia and endometrial carcinoma. Estrogen should be prescribed with an appropriate dosage of a progestin in women with intact uteri in order to prevent endometrial hyperplasia/carcinoma.

During the conduct of a pivotal clinical study in an open-labeled study of 369 women (mean age = 49) with endogenous estrogen deficiency associated with menopausal symptoms (see **CLINICAL TRIALS** Section in Product Monograph), endometrial biopsies were conducted in a subset of 32 subjects prior to and after therapy. Prior to therapy eleven (11) samples were considered abnormal: cystic hyperplasia (4), adenomatous hyperplasia (6) and mixed-inactive hyperplasia (1). One (1) sample biopsy remained abnormal after 11 months of treatment with ESTRACE®, changing from cystic hyperplasia to benign cystic hyperplasia.

In a second pivotal clinical study on the prevention of early postmenopausal bone loss (see **CLINICAL TRIALS** Section in Product Monograph), exit endometrial biopsy specimens were obtained for 21 subjects. Abnormalities consistent with estrogen stimulation of the endometrium were found in 27% of these subjects. Two (2) subjects had progression to the point of adenomatous hyperplasia and one (1) subject had atypical nuclear changes. No subjects, however, developed adenocarcinoma of the endometrium.

#### 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.

#### 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 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

Women using hormone replacement therapy 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 may have to be discontinued.

#### Endocrine and Metabolism

##### Glucose and lipid metabolism

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 hyperlipidemias or porphyria need special surveillance. Lipid-lowering measures are recommended additionally, before treatment is started.

#### Calcium and phosphorus metabolism

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.

#### Genitourinary

##### Vaginal bleeding

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.

##### Uterine leiomyoma

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

##### Endometriosis

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

#### Hematologic

##### Venous thromboembolism

Available epidemiological data indicate that use of estrogen with or without progestin is associated with an increased risk of developing venous thromboembolism (VTE).

In the *estrogen plus progestin* arm of the WHI trial, among 10,000 women on combined HRT over a one-year period, there were 18 more cases of venous thromboembolism, including 8 more cases of pulmonary embolism.

In the *estrogen-alone* arm of the WHI trial, among 10,000 women on estrogen therapy over a one-year period, there were 7 more cases of venous thromboembolism, although there was no statistically significant difference in the rate of pulmonary embolism.

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 >30 kg/m<sup>2</sup>). The risk of VTE also increases with age and smoking. The risk of VTE may be temporarily increased with prolonged immobilization, major surgery or trauma. 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, given the risk of long-term disability or fatality.

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.

#### Hepatic/Biliary/Pancreatic

##### Gallbladder diseases

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

##### 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 the section under **Monitoring and Laboratory Tests**.

#### Neurologic

##### Cerebrovascular insufficiency

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

##### Dementia

Available epidemiological data indicate that the use of combined *estrogen plus progestin* in women age 65 and over may increase the risk of developing probable dementia. The Women's Health Initiative Memory Study (WHIMS), a clinical substudy of the WHI, was designed to assess whether postmenopausal hormone replacement therapy (*estrogen plus progestin* or *estrogen-alone*) reduces the risk of dementia in women aged 65 and over and free of dementia at baseline.

In the *estrogen plus progestin* arm of the WHIMS (n=4532), women with an intact uterus were treated with daily 0.625 mg conjugated equine estrogens (CEE) plus 2.5 mg medroxyprogesterone acetate (MPA) or placebo for an average of 4.05 years. The results, when extrapolated to 10,000 women treated over a one-year period showed:

- 23 more cases of probable dementia (45 on combined HRT versus 22 on placebo).

In the *estrogen-alone* arm of the WHIMS (n=2947), women with prior hysterectomy were treated with daily 0.625 mg CEE or placebo for an average of 5.21 years. The results, when extrapolated to 10,000 women treated over a one-year period showed:

- 12 more cases of probable dementia (37 on *estrogen-alone* versus 25 on placebo), although this difference did not reach statistical significance.

When data from the *estrogen plus progestin* arm of the WHIMS and the *estrogen-alone* arm of the WHIMS were combined, as per the original WHIMS protocol, in 10,000 women over a one-year period, there were:

- 18 more cases of probable dementia (41 on *estrogen plus progestin* or *estrogen-alone* versus 23 on placebo).

## Renal

### Fluid retention

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 an 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.

### Special Populations

**Geriatrics (> 65 years of age):** The use of combined *estrogen plus progestin* in women aged 65 and over may increase the risk of developing probable dementia (see **WARNINGS AND PRECAUTIONS, Neurologic**).

### Monitoring and Laboratory Tests

Before ESTRACE® 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 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.

### Adverse Reactions

#### Adverse Drug Reaction Overview

See **WARNINGS AND PRECAUTIONS** regarding potential induction of malignant neoplasms and adverse effects similar to those of oral contraceptives.

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

- **Blood and lymphatic system disorders** Altered coagulation tests (see **WARNINGS AND PRECAUTIONS, Drug-Laboratory Test Interactions**).
- **Cardiac disorders** Palpitations; increase in blood pressure (see **WARNINGS AND PRECAUTIONS**); coronary thrombosis.
- **Congenital, Familial and Genetic disorders** Precipitation or aggravation of porphyria cutanea tarda in predisposed individuals.
- **Endocrine disorders** Increased blood sugar levels; decreased glucose tolerance.
- **Eye disorders** Neuro-ocular lesions (e.g., retinal thrombosis, 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; anorexia; changes in body weight; 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; endometrial hyperplasia; increase in size of uterine leiomyoma; vaginal candidiasis; pre-menstrual-like syndrome; reactivation of endometriosis; changes in cervical erosion and amount of cervical secretion; increased cervical mucus; breast swelling, tenderness and secretion.
- **Skin and subcutaneous tissue disorders** Chloasma or melasma, which may persist when drug is discontinued; pigmentation of skin; erythema multiforme; erythema nodosum; haemorrhagic eruption; itching, allergic reactions and rashes; loss of scalp hair; hirsutism and acne.
- **Vascular disorders** Isolated cases of: thrombophlebitis; thromboembolic disorders.

### Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates. The following table summarizes the adverse events reported in a controlled, randomized, double-blind study with ESTRACE® for the treatment of osteoporosis in 64 post-menopausal women. ESTRACE® was administered in a cyclic manner for up to 18 months with an option to continue for an additional 6 months.

**Table 1: Reported Events for more than one patient per dose group: Symptoms by Treatment assignment symptom**

	0.5 mg Estrace n=15(%)	2.0mg Estrace® n=16(%)	2.0 mg Estrace n=16(%)	Placebo n=16(%)
<b>Gastrointestinal Disorders</b>				
nausea	0	0	0	2 (13%)
constipation	2 (13%)	1 (6%)	0	1 (6%)
<b>General Disorders &amp; Administration Site Conditions</b>				
asthenia	0	0	2 (13%)	1 (6%)
<b>Investigations</b>				
weight increased	3 (20%)	3 (19%)	2 (13%)	1 (6%)
<b>Nervous System Disorders</b>				
headache	0	0	1 (6%)	2 (13%)
<b>Psychiatric Disorders</b>				
nervousness	1 (7%)	2 (13%)	5 (31%)	2 (13%)
insomnia	0	1 (6%)	2 (13%)	2 (13%)
depression	2 (13%)	0	3 (19%)	3 (19%)
libido decreased	0	0	0	2 (13%)
<b>Renal &amp; Urinary Disorders</b>				
oedema	2 (13%)	1 (6%)	2 (13%)	1 (6%)
<b>Reproductive System &amp; Breast disorders</b>				
menopausal systems <sup>*</sup>	10 (67%)	11 (69%)	11 (69%)	13 (81%)
vaginal haemorrhage	2 (13%)*	7 (44%)*	9 (56%)*	1 (6%)
vaginitis	1 (7%)	2 (13%)	0	0
uterine spasm	0	0	2 (13%)	0

\* statistically significant at 5% level (Fisher's exact test)

† statistically significant at 5% level (Fisher's exact test); † according to MEDRA dictionary, including symptoms if adverse symptoms persist, the prescription of HRT should be reconsidered

### Drug Interactions

#### Overview

Estrogens may diminish the effectiveness of anticoagulants, antidiabetic and antihypertensive agents. Preparations inducing liver enzymes, (e.g. barbiturates, hydantoins, carbamazepine, meprobamate, phenylbutazone or rifampicin) may interfere with the activity of orally administered estrogens.

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

The following contains information on drug interactions with ethinyl estradiol-containing products that have been reported in the published 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 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 increase AUC values for ethinyl estradiol by 20 percent.
- Drug products containing ethinyl estradiol may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporin, prednisolone, and theophylline have been reported with concomitant administration of certain drugs 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, salicylic acid, morphine and clofibrate acid have been noted when these drugs were administered with certain ethinyl estradiol containing drug products.

### Drug-Drug Interactions

Possible drug-drug interactions with ESTRACE® specifically have not been established.

### Drug-Food Interactions

The effect of food or beverages on the use of ESTRACE® has not been established.

### Drug-Herb Interactions

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

### Drug-Laboratory Test Interactions

The results of certain endocrine and liver function tests may be affected by estrogen-containing products. increased prothrombin time and partial thromboplastin time; increased levels of fibrinogen and fibrinogen activity; increased coagulation factors VII, VIII, IX, X; decreased antithrombin III (although following administration of ESTRACE for 28 days no effect on antithrombin III levels was seen); increased norepinephrine-induced platelet aggregability; increased thyroxine-binding globulin (TBG) (although TBG was not affected in clinical trials with ESTRACE, leading to increased circulating total thyroid hormone (T<sub>4</sub>) as measured by column or radioimmunoassay; free T<sub>3</sub> resin uptake is decreased, reflecting the elevated TBG, free T<sub>4</sub> 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 serum folate concentration; increased serum triglyceride and phospholipid concentrations; - impaired glucose tolerance.

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 when relevant specimens are submitted.

### Drug-Lifestyle Interactions

The effect of lifestyle choices (e.g. smoking) on the use of ESTRACE® has not been established.

### DOSAGE AND ADMINISTRATION

#### Dosing Considerations

The lowest dose of estrogen required to prevent menopausal symptoms and to prevent development of osteoporosis should be used. ESTRACE® should be taken at the same time each day.

ESTRACE® should be taken as soon as possible after missing a dose. However the missed dose should be skipped if it is almost time to take the next dose. Patients should be advised not to double the dose.

#### Recommended Dose and Dosage Adjustment

In general, estrogen is usually administered cyclically for the first 21 to 25 days of each month. In patients with intact uteri a progestin should be sequentially administered for the last 12 to 14 days of estrogen administration in order to prevent development of endometrial hyperplasia/carcinoma as a result of estrogen stimulation. In hysterectomized patients, estrogen alone should be given continuously. Menopausal symptoms: Treatment of menopausal symptoms is usually initiated with 1 mg ESTRACE® tablet per day. Thereafter, the dosage should be adjusted to the needs of the individual. Attempts to taper or discontinue the medication should be made at 3 to 6 month intervals. For prevention of osteoporosis: Prophylactic therapy with ESTRACE® to prevent postmenopausal bone loss should be initiated with 0.5 mg ESTRACE® tablet per day as soon as possible after menopause. The dose may be titrated upward and downward based on the patient's clinical status and plasma estradiol levels. Ideally, plasma estradiol levels should be maintained around 50 pg/mL.

#### DOSAGE FORMS, COMPOSITION AND PACKAGING

##### Dosing Considerations

ESTRACE® tablets are taken orally.

ESTRACE® 0.5 mg: Each tablet contains 0.5 mg of micronized 17β-estradiol. Nonmedicinal ingredients: acacia, cornstarch, dibasic calcium phosphate, lactose, magnesium stearate, silicon dioxide, talc. Tablet is white with MJ logo and "021" on one side and scored on the reverse.

ESTRACE® 1 mg: Each tablet contains 1 mg of micronized 17β-estradiol. Nonmedicinal ingredients: acacia, cornstarch, dibasic calcium phosphate, lactose, magnesium stearate, silicon dioxide, talc and colour dyes (FD&C Blue #1 and D&C Red #27 aluminum lake). Tablet is lavender with MJ logo and "755" on one side and scored on the reverse.

ESTRACE® 2 mg: Each tablet contains 2 mg of micronized 17β-estradiol. Nonmedicinal ingredients: acacia, cornstarch, dibasic calcium phosphate, lactose, magnesium stearate, silicon dioxide, talc and colour dyes (FD&C Blue #1 and FD&C Yellow #5 aluminum lake (tartrazine)). Tablet is turquoise with MJ logo and "756" on one side and scored on the reverse.

ESTRACE® tablets are available as round, flat-faced, bevel-edged compressed tablets containing 17β-estradiol in bottles of 100.

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#### Product Monograph available on request

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