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2 Rev Jan 2005
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Physician Labeling

ESTRATEST®‡
and
ESTRATEST® H.S.‡

R_x only

(Esterified Estrogens and Methyltestosterone) Tablets

4

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of “natural” estrogens results in a different endometrial risk profile than synthetic estrogens at equivalent estrogen doses. (See **WARNINGS, Malignant Neoplasms, Endometrial Cancer.**)

CARDIOVASCULAR AND OTHER RISKS

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease. (See **WARNINGS, Cardiovascular Disorders.**)

The Women’s Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

The Women’s Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with oral conjugated estrogens plus medroxyprogesterone acetate relative to placebo. It is unknown whether this finding applies to younger postmenopausal women or to women taking estrogen alone therapy. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

5
6 **DESCRIPTION**

7 ESTRATEST® Tablets: Each dark green, capsule shaped, sugar-coated oral tablet contains:
8 1.25 mg of Esterified Estrogens, USP and 2.5 mg of Methyltestosterone, USP.

9
10 ESTRATEST® H.S. (Half-Strength) Tablets: Each light green, capsule shaped, sugar-coated oral
11 tablet contains: 0.625 mg of Esterified Estrogens, USP and 1.25 mg of Methyltestosterone, USP.

12 13 **Esterified Estrogens**

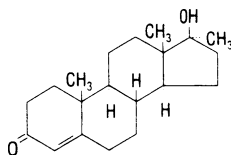
14 Esterified Estrogens, USP is a mixture of the sodium salts of the sulfate esters of the estrogenic
15 substances, principally estrone, that are of the type excreted by pregnant mares. Esterified
16 Estrogens contain not less than 75.0 percent and not more than 85.0 percent of sodium estrone
17 sulfate, and not less than 6.0 percent and not more than 15.0 percent of sodium equilin sulfate, in
18 such proportion that the total of these two components is not less than 90.0 percent.

19 20 **Methyltestosterone**

21 Methyltestosterone, USP is an androgen. Androgens are derivatives of cyclopentano-
22 perhydrophenanthrene. Endogenous androgens are C-19 steroids with a side chain at C-17, and
23 with two angular methyl groups. Testosterone is the primary endogenous androgen.
24 Fluoxymesterone and methyltestosterone are synthetic derivatives of testosterone.

25
26 Methyltestosterone is a white to light yellow crystalline substance that is virtually insoluble in
27 water but soluble in organic solvents. It is stable in air but decomposes in light.

28
29 Methyltestosterone structural formula:



37
38 Androst-4-en-3-one, 17-hydroxy-17-methyl-, (17•)-

39
40 ESTRATEST and ESTRATEST H.S. Tablets contain the following inactive ingredients:
41 acacia, acetylated monoglycerides, calcium carbonate, carboxymethylcellulose sodium, carnauba
42 wax NF, citric acid, colloidal silicon dioxide, gelatin, iron oxide, lactose, magnesium stearate,
43 methylparaben, microcrystalline cellulose, pharmaceutical glaze, povidone, propylene glycol,
44 propylparaben, shellac glaze, sodium benzoate, sodium bicarbonate, sorbic acid, starch, sucrose,
45 talc, titanium dioxide, and tribasic calcium phosphate.

46
47 ESTRATEST Tablets also contain: FD&C Blue No. 1 Lake, FD&C Yellow No. 6 Lake, and
48 D&C Yellow No. 10 Lake.

49

50 ESTRATEST H.S. Tablets also contain: D&C Yellow No. 10 Lake, FD&C Blue No. 1 Lake,
51 FD&C Blue No. 2 Lake, FD&C Yellow No. 6 Lake, and FD&C Red No. 40 Lake.

52

53 **CLINICAL PHARMACOLOGY**

54 **Estrogens:** Endogenous estrogens are largely responsible for the development and
55 maintenance of the female reproductive system and secondary sexual characteristics. Although
56 circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is
57 the principal intracellular human estrogen and is substantially more potent than its metabolites,
58 estrone and estriol at the receptor level.

59

60 The primary source of estrogen in normally cycling adult women is the ovarian follicle,
61 which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle.
62 After menopause, most endogenous estrogen is produced by conversion of androstenedione,
63 secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate
64 conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal
65 women.

66

67 Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date,
68 two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

69

70 Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing
71 hormone (LH) and follicle stimulating hormone (FSH), through a negative feedback mechanism.
72 Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.

73

74 *Estrogen Pharmacokinetics*

75 *Distribution*

76 The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are
77 widely distributed in the body and are generally found in higher concentrations in the sex
78 hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding
79 globulin (SHBG) and albumin.

80

81 *Metabolism*

82 Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating
83 estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations
84 take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be
85 converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic
86 recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates
87 into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women,
88 a significant proportion of the circulating estrogens exist as sulfate conjugates, especially estrone
89 sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

90

91 *Excretion*

92 Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate
93 conjugates.

94

95 **Drug Interactions**

96 *In vitro* and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome
 97 P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug
 98 metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (*Hypericum perforatum*),
 99 phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens,
 100 possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding
 101 profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole,
 102 ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in
 103 side effects.

104

105 **Clinical Studies**106 **Women's Health Initiative Studies**

107 The Women's Health Initiative (WHI) enrolled a total of 27,000 predominantly healthy
 108 postmenopausal women to assess the risks and benefits of either the use of oral 0.625 mg
 109 conjugated estrogens (CE) per day alone or the use of oral 0.625 mg conjugated estrogens plus
 110 2.5 mg medroxyprogesterone acetate (MPA) per day compared to placebo in the prevention of
 111 certain chronic diseases. The primary endpoint was the incidence of coronary heart disease
 112 (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the
 113 primary adverse outcome studied. A "global index" included the earliest occurrence of CHD,
 114 invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer,
 115 hip fracture, or death due to other cause. The study did not evaluate the effects of CE or
 116 CE/MPA on menopausal symptoms.

117

118 The CE-only substudy has concluded. The impact of those results are under review. The
 119 CE/MPA substudy was stopped early because, according to the predefined stopping rule, the
 120 increased risk of breast cancer and cardiovascular events exceeded the specified benefits included
 121 in the "global index." Results of the CE/MPA substudy, which included 16,608 women (average
 122 age of 63 years, range 50 to 79; 83.9% White, 6.5% Black, 5.5% Hispanic), after an average
 123 follow-up of 5.2 years are presented in Table 1 below.

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TABLE 1
Relative and Absolute Risk Seen in the CE/MPA Substudy of WHI^a

Event ^c	Relative Risk CE/MPA versus placebo at 5.2 Years (95% CI*)	Placebo n = 8102	CE/MPA n = 8506
		Absolute Risk per 10,000 Women-years	
CHD events	1.29 (1.02-1.63)	30	37
<i>Non-fatal MI</i>	1.32 (1.02-1.72)	23	30
<i>CHD death</i>	1.18 (0.70-1.97)	6	7
Invasive breast cancer ^b	1.26 (1.00-1.59)	30	38
Stroke	1.41 (1.07-1.85)	21	29
Pulmonary embolism	2.13 (1.39-3.25)	8	16
Colorectal cancer	0.63 (0.43-0.92)	16	10
Endometrial cancer	0.83 (0.47-1.47)	6	5
Hip fracture	0.66 (0.45-0.98)	15	10

Death due to causes other than the events above	0.92 (0.74-1.14)	40	37
Global Index ^c	1.15 (1.03-1.28)	151	170
Deep vein thrombosis ^d	2.07 (1.49-2.87)	13	26
Vertebral fractures ^d	0.66 (0.44-0.98)	15	9
Other osteoporotic fractures ^d	0.77 (0.69-0.86)	170	131

^a adapted from *JAMA*, 2002; 288:321-333

^b includes metastatic and non-metastatic breast cancer with the exception of *in situ* breast cancer

^c a subset of the events was combined in a "global index," defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes

^d not included in Global Index

* nominal confidence intervals unadjusted for multiple looks and multiple comparisons

For those outcomes included in the "global index," the absolute excess risks per 10,000 women-years in the group treated with CE/MPA were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality. (See **BOXED WARNINGS**, **WARNINGS**, and **PRECAUTIONS**.)

Women's Health Initiative Memory Study

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47% were age 65 to 69 years, 35% were 70 to 74 years, and 18% were 75 years of age and older) to evaluate the effects of CE/MPA (0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate) on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 4 years, 40 women in the estrogen/progestin group (45 per 10,000 women-years) and 21 in the placebo group (22 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the hormone therapy group was 2.05 (95% CI, 1.21 to 3.48) compared to placebo. Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS** and **WARNINGS, Dementia**.)

Androgens: Endogenous androgens are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis, and scrotum; the development of male hair distribution, such as beard, pubic, chest, and axillary hair, laryngeal enlargement, vocal cord thickening, alterations in body musculature, and fat distribution. Drugs in this class also cause retention of nitrogen, sodium, potassium, phosphorus, and decreased urinary excretion of calcium. Androgens have been reported to increase protein anabolism and decrease protein catabolism. Nitrogen balance is improved only when there is sufficient intake of calories and protein. Androgens are responsible for the growth spurt of adolescence and for the eventual termination of linear growth which is brought about by fusion of the epiphyseal growth centers. In children,

167 exogenous androgens accelerate linear growth rates, but may cause a disproportionate advancement
168 in bone maturation. Use over long periods may result in fusion of the epiphyseal growth centers
169 and termination of growth process. Androgens have been reported to stimulate the production of
170 red blood cells by enhancing the production of erythropoietic stimulating factor.

171

172 ***Androgen Pharmacokinetics***

173 Testosterone given orally is metabolized by the gut and 44 percent is cleared by the liver in the first
174 pass. Oral doses as high as 400 mg per day are needed to achieve clinically effective blood levels
175 for full replacement therapy. The synthetic androgens (methyltestosterone and fluoxymesterone)
176 are less extensively metabolized by the liver and have longer half-lives. They are more suitable
177 than testosterone for oral administration.

178

179 Testosterone in plasma is 98 percent bound to a specific testosterone-estradiol binding globulin,
180 and about 2 percent is free. Generally, the amount of this sex-hormone binding globulin in the
181 plasma will determine the distribution of testosterone between free and bound forms, and the free
182 testosterone concentration will determine its half-life.

183

184 About 90 percent of a dose of testosterone is excreted in the urine as glucuronic and sulfuric
185 acid conjugates of testosterone and its metabolites; about 6 percent of a dose is excreted in the
186 feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver.
187 Testosterone is metabolized to various 17-keto steroids through two different pathways. There are
188 considerable variations of the half-life of testosterone as reported in the literature, ranging from 10
189 to 100 minutes.

190

191 In many tissues the activity of testosterone appears to depend on reduction to
192 dihydrotestosterone, which binds to cytosol receptor proteins. The steroid-receptor complex is
193 transported to the nucleus where it initiates transcription events and cellular changes related to
194 androgen action.

195

196 **INDICATIONS AND USAGE**

197 ESTRATEST and ESTRATEST H.S. Tablets are indicated in the:

- 198 • Treatment of moderate to severe vasomotor symptoms associated with the menopause in those
199 patients not improved by estrogens alone. (There is no evidence that estrogens are effective for
200 nervous symptoms or depression without associated vasomotor symptoms, and they should not
201 be used to treat such conditions.)

202

203 ESTRATEST and ESTRATEST H.S. Tablets have not been shown to be effective for any
204 purpose during pregnancy and its use may cause severe harm to the fetus.

205

206 **CONTRAINDICATIONS**

207 ESTRATEST and ESTRATEST H.S. Tablets should not be used in women with any of the
208 following conditions:

- 209 1. Undiagnosed abnormal genital bleeding.
- 210 2. Known, suspected, or history of cancer of the breast.

- 211 3. Known or suspected estrogen-dependent neoplasia.
212 4. Active deep vein thrombosis, pulmonary embolism or history of these conditions.
213 5. Active or recent (e.g., within the past year) arterial thromboembolic disease (e.g., stroke,
214 myocardial infarction).
215 6. Liver dysfunction or disease.
216 7. ESTRATEST and ESTRATEST H.S. Tablets should not be used in patients with known
217 hypersensitivity to its ingredients.
218 8. Known or suspected pregnancy. There is no indication for ESTRATEST and ESTRATEST
219 H.S. Tablets in pregnancy. There appears to be little or no increased risk of birth defects in
220 children born to women who have used estrogens and progestins from oral contraceptives
221 inadvertently during early pregnancy. (See **PRECAUTIONS.**)
222

223 Methyltestosterone should not be used in:

- 224 1. The presence of severe liver damage.
225 2. Pregnancy and in breast-feeding mothers because of the possibility of masculinization of the
226 female fetus or breast-fed infant.
227

228 **WARNINGS**

229 See **BOXED WARNINGS.**
230

231 **Warnings Associated with Estrogens**

232 **Cardiovascular Disorders**

233 Estrogen and estrogen/progestin therapy has been associated with an increased risk of
234 cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and
235 pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be
236 suspected, estrogens should be discontinued immediately.
237

238 Risk factors for arterial vascular disease (e.g., hypertension, diabetes mellitus, tobacco use,
239 hypercholesterolemia, and obesity) and/or venous thromboembolism (e.g., personal history or
240 family history of VTE, obesity, and systemic lupus erythematosus) should be managed
241 appropriately.
242

243 **Coronary Heart Disease and Stroke:** In the Women's Health Initiative (WHI) study, an increase
244 in the number of myocardial infarctions and strokes was observed in women receiving CE
245 compared to placebo. The CE-only substudy has concluded. The impact of those results are
246 under review. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)
247

248 In the CE/MPA substudy of WHI, an increased risk of coronary heart disease (CHD) events
249 (defined as nonfatal myocardial infarction and CHD death) was observed in women receiving
250 CE/MPA compared to women receiving placebo (37 versus 30 per 10,000 women-years). The
251 increase in risk was observed in year 1 and persisted.
252

253 In the same substudy of WHI, an increased risk of stroke was observed in women receiving
254 CE/MPA compared to women receiving placebo (29 versus 21 per 10,000 women-years). The

255 increase in risk was observed after the first year and persisted.
256

257 In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years)
258 a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and
259 Estrogen/Progestin Replacement Study; HERS) treatment with CE/MPA (0.625 mg/2.5 mg per
260 day) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years,
261 treatment with CE/MPA did not reduce the overall rate of CHD events in postmenopausal
262 women with established coronary heart disease. There were more CHD events in the CE/MPA-
263 treated group than in the placebo group in year 1, but not during the subsequent years. Two
264 thousand three hundred and twenty one women from the original HERS trial agreed to participate
265 in an open-label extension of HERS, HERS II. Average follow-up in HERS II was an additional
266 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women
267 in the CE/MPA group and the placebo group in HERS, HERS II, and overall.
268

269 Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to
270 treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in
271 men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and
272 thrombophlebitis.
273

274 ***Venous Thromboembolism (VTE):*** In the Women's Health Initiative (WHI) study, an increase
275 in VTE was observed in women receiving CE compared to placebo. The CE-only substudy has
276 concluded. The impact of those results are under review. (See **CLINICAL**
277 **PHARMACOLOGY, Clinical Studies.**)
278

279 In the CE/MPA substudy of WHI, a 2-fold greater rate of VTE, including deep venous
280 thrombosis and pulmonary embolism, was observed in women receiving CE/MPA compared to
281 women receiving placebo. The rate of VTE was 34 per 10,000 women-years in the CE/MPA
282 group compared to 16 per 10,000 women-years in the placebo group. The increase in VTE risk
283 was observed during the first year and persisted.
284

285 If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type
286 associated with an increased risk of thromboembolism, or during periods of prolonged
287 immobilization.
288

289 **Malignant Neoplasms**

290 ***Endometrial Cancer:*** The use of unopposed estrogens in women with intact uteri has been
291 associated with an increased risk of endometrial cancer. The reported endometrial cancer risk
292 among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears
293 dependent on duration of treatment and on estrogen dose. Most studies show no significant
294 increased risk associated with use of estrogens for less than one year. The greatest risk appears
295 associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more
296 and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is
297 discontinued.
298

299 Clinical surveillance of all women taking estrogen/progestin combinations is important.
300 Adequate diagnostic measures, including endometrial sampling when indicated, should be
301 undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal
302 vaginal bleeding. There is no evidence that the use of natural estrogens results in a different
303 endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin
304 to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be
305 a precursor to endometrial cancer.

306
307 **Breast Cancer:** The use of estrogens and progestins by postmenopausal women has been
308 reported to increase the risk of breast cancer. The most important randomized clinical trial
309 providing information about this issue is the Women's Health Initiative (WHI) substudy of
310 CE/MPA. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**) The results from
311 observational studies are generally consistent with those of the WHI clinical trial and report no
312 significant variation in the risk of breast cancer among different estrogens or progestins, doses, or
313 routes of administration.

314
315 The CE/MPA substudy of WHI reported an increased risk of breast cancer in women who
316 took CE/MPA for a mean follow-up of 5.6 years. Observational studies have also reported an
317 increased risk for estrogen/progestin combination therapy, and a smaller increased risk for
318 estrogen alone therapy, after several years of use. In the WHI trial and from observational
319 studies, the excess risk increased with duration of use. From observational studies, the risk
320 appeared to return to baseline in about five years after stopping treatment. In addition,
321 observational studies suggest that the risk of breast cancer was greater, and became apparent
322 earlier, with estrogen/progestin combination therapy as compared to estrogen alone therapy.

323
324 In the CE/MPA substudy, 26% of the women reported prior use of estrogen alone and/or
325 estrogen/progestin combination hormone therapy. After a mean follow-up of 5.6 years during the
326 clinical trial, the overall relative risk of invasive breast cancer was 1.24 (95% confidence interval
327 1.01-1.54), and the overall absolute risk was 41 versus 33 cases per 10,000 women-years, for
328 CE/MPA compared with placebo. Among women who reported prior use of hormone therapy,
329 the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases
330 per 10,000 women-years, for CE/MPA compared with placebo. Among women who reported no
331 prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the
332 absolute risk was 40 versus 36 cases per 10,000 women-years for CE/MPA compared with
333 placebo. In the same substudy, invasive breast cancers were larger and diagnosed at a more
334 advanced stage in the CE/MPA group compared with the placebo group. Metastatic disease was
335 rare with no apparent difference between the two groups. Other prognostic factors such as
336 histologic subtype, grade and hormone receptor status did not differ between the groups.

337
338 The use of estrogen plus progestin has been reported to result in an increase in abnormal
339 mammograms requiring further evaluation. All women should receive yearly breast examinations
340 by a healthcare provider and perform monthly breast self-examinations. In addition,
341 mammography examinations should be scheduled based on patient age, risk factors, and prior
342 mammogram results.

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Dementia

In the Women's Health Initiative Memory Study (WHIMS), 4,532 generally healthy postmenopausal women 65 years of age and older were studied, of whom 35% were 70 to 74 years of age and 18% were 75 or older. After an average follow-up of 4 years, 40 women being treated with CE/MPA (1.8%, n = 2,229) and 21 women in the placebo group (0.9%, n = 2,303) received diagnoses of probable dementia. The relative risk for CE/MPA versus placebo was 2.05 (95% confidence interval 1.21 – 3.48), and was similar for women with and without histories of menopausal hormone use before WHIMS. The absolute risk of probable dementia for CE/MPA versus placebo was 45 versus 22 cases per 10,000 women-years, and the absolute excess risk for CE/MPA was 23 cases per 10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women. (See **CLINICAL PHARMACOLOGY, Clinical Studies** and **PRECAUTIONS, Geriatric Use**.)

The estrogen alone substudy of the Women's Health Initiative Memory Study has concluded. It is unknown whether these findings apply to estrogen alone.

Gallbladder Disease

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

Glucose Tolerance

A worsening of glucose tolerance has been observed in a significant percentage of patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed while receiving estrogens.

Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

Visual Abnormalities

Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

Warnings Associated with Methyltestosterone

In patients with breast cancer, androgen therapy may cause hypercalcemia by stimulating osteolysis. In this case the drug should be discontinued.

Prolonged use of high doses of androgens has been associated with the development of peliosis hepatis and hepatic neoplasms including hepatocellular carcinoma. (See **PRECAUTIONS – Carcinogenesis (Androgens)**.) Peliosis hepatis can be a life-threatening or fatal complication.

387
388 Cholestatic hepatitis and jaundice occur with 17-alpha-alkylandrogens at a relatively low dose.
389 If cholestatic hepatitis with jaundice appears or if liver function tests become abnormal, the
390 androgen should be discontinued and the etiology should be determined. Drug-induced jaundice is
391 reversible when the medication is discontinued.
392

393 Edema with or without heart failure may be a serious complication in patients with preexisting
394 cardiac, renal, or hepatic disease. In addition to discontinuation of the drug, diuretic therapy may be
395 required.
396

397 **PRECAUTIONS**

398 **General Precautions Associated with Estrogens**

399 *Addition of a progestin when a woman has not had a hysterectomy:* Studies of the addition of
400 a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a
401 continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be
402 induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial
403 cancer.
404

405 There are, however, possible risks that may be associated with the use of progestins with
406 estrogens compared to estrogen-alone regimens. These include a possible increased risk of breast
407 cancer.
408

409 *Elevated blood pressure:* In a small number of case reports, substantial increases in blood
410 pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized,
411 placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen.
412 Blood pressure should be monitored at regular intervals with estrogen use.
413

414 *Hypertriglyceridemia:* In patients with pre-existing hypertriglyceridemia, estrogen therapy may
415 be associated with elevations of plasma triglycerides leading to pancreatitis and other
416 complications.
417

418 *Impaired liver function and past history of cholestatic jaundice:* Estrogens may be poorly
419 metabolized in patients with impaired liver function. For patients with a history of cholestatic
420 jaundice associated with past estrogen use or with pregnancy, caution should be exercised and in
421 the case of recurrence, medication should be discontinued.
422

423 *Hypothyroidism:* Estrogen administration leads to increased thyroid-binding globulin (TBG)
424 levels. Patients with normal thyroid function can compensate for the increased TBG by making
425 more thyroid hormone, thus maintaining free T4 and T3 serum concentrations in the normal
426 range. Patients dependent on thyroid hormone replacement therapy who are also receiving
427 estrogens may require increased doses of their thyroid replacement therapy. These patients
428 should have their thyroid function monitored in order to maintain their free thyroid hormone
429 levels in an acceptable range.
430

431 *Fluid retention:* Because estrogens may cause some degree of fluid retention, patients with

432 conditions that might be influenced by this factor, such as a cardiac or renal dysfunction, warrant
433 careful observation when estrogens are prescribed.

434
435 **Hypocalcemia:** Estrogens should be used with caution in individuals with severe hypocalcemia.

436
437 **Ovarian cancer:** The CE/MPA substudy of WHI reported that estrogen plus progestin increased
438 the risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian
439 cancer for CE/MPA versus placebo was 1.58 (95% confidence interval 0.77 – 3.24) but was not
440 statistically significant. The absolute risk for CE/MPA versus placebo was 4.2 versus 2.7 cases
441 per 10,000 women-years. In some epidemiologic studies, the use of estrogen alone, in particular
442 for 10 or more years, has been associated with an increased risk of ovarian cancer. Other
443 epidemiologic studies have not found these associations.

444
445 **Exacerbation of endometriosis:** Endometriosis may be exacerbated with administration of
446 estrogens. A few cases of malignant transformation of residual endometrial implants have been
447 reported in women treated post-hysterectomy with estrogen alone therapy. For patients known to
448 have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

449
450 **Exacerbation of other conditions:** Estrogens may cause an exacerbation of asthma, diabetes
451 mellitus, epilepsy, migraine or porphyria, systemic lupus erythematosus, and hepatic
452 hemangiomas and should be used with caution in women with these conditions.

453 454 **General Precautions Associated with Methyltestosterone**

- 455 1. Women should be observed for signs of virilization (deepening of the voice, hirsutism, acne,
456 clitoromegaly, and menstrual irregularities). Discontinuation of drug therapy at the time of
457 evidence of mild virilism is necessary to prevent irreversible virilization. Such virilization is
458 usual following androgen use at high doses.
- 459 2. Prolonged dosage of androgen may result in sodium and fluid retention. This may present a
460 problem, especially in patients with compromised cardiac reserve or renal disease.
- 461 3. Hypersensitivity may occur rarely.
- 462 4. Protein-bound iodine (PBI) may be decreased in patients taking androgens.
- 463 5. Hypercalcemia may occur. If this does occur, the drug should be discontinued.

464 465 466 467 468 **Patient Information (Estrogens)**

469 Physicians are advised to discuss the PATIENT INFORMATION leaflet with patients for whom
470 they prescribe ESTRATEST and ESTRATEST H.S. Tablets.

471 472 473 **Patient Information (Androgens)**

474 The physician should instruct patients to report any of the following side effects of androgens:

475
476 **Women:** Hoarseness, acne, changes in menstrual periods, or more hair on the face.

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All Patients: Any nausea, vomiting, changes in skin color or ankle swelling.

Laboratory Tests (Estrogens)

Estrogen administration should be initiated at the lowest dose approved for the indication and then guided by clinical response rather than by serum hormone levels (e.g., estradiol, FSH).

Laboratory Tests (Androgens)

1. Women with disseminated breast carcinoma should have frequent determination of urine and serum calcium levels during the course of androgen therapy. (See **WARNINGS**.)
2. Because of the hepatotoxicity associated with the use of 17-alpha-alkylated androgens, liver function tests should be obtained periodically.
3. Hemoglobin and hematocrit should be checked periodically for polycythemia in patients who are receiving high doses of androgens.

Drug/Laboratory Test Interactions (Estrogens)

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antifactor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.
2. Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone levels as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.
3. Other binding proteins may be elevated in serum (i.e., corticosteroid binding globulin (CBG), sex hormone binding globulin (SHBG)) leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).
4. Increased plasma HDL and HDL₂ cholesterol subfraction concentrations, reduced LDL cholesterol concentration, increased triglycerides levels.
5. Impaired glucose tolerance.
6. Reduced response to metyrapone test.

Drug Interactions (Androgens)

521 **Anticoagulants:** C-17 substituted derivatives of testosterone, such as methandrostenolone, have
522 been reported to decrease the anticoagulant requirements of patients receiving oral anticoagulants.
523 Patients receiving oral anticoagulant therapy require close monitoring, especially when androgens
524 are started or stopped.

525
526 **Oxyphenbutazone:** Concurrent administration of oxyphenbutazone and androgens may result in
527 elevated serum levels of oxyphenbutazone.

528
529 **Insulin:** In diabetic patients, the metabolic effects of androgens may decrease blood glucose and
530 insulin requirements.

531

532 **Drug/Laboratory Test Interferences (Androgens)**

533 Androgens may decrease levels of thyroxine-binding globulin, resulting in decreased T4 serum
534 levels and increased resin uptake of T3 and T4. Free thyroid hormone levels remain unchanged,
535 however, and there is no clinical evidence of thyroid dysfunction.

536

537 **Carcinogenesis, Mutagenesis, Impairment of Fertility (Estrogens)**

538 Long-term continuous administration of estrogen, with and without progestin, in women with
539 and without a uterus, has shown an increased risk of endometrial cancer, breast cancer, and
540 ovarian cancer. (See **BOXED WARNINGS, WARNINGS** and **PRECAUTIONS**.)

541

542 Long-term continuous administration of natural and synthetic estrogens in certain animal
543 species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and
544 liver.

545

546 **Carcinogenesis (Androgens)**

547 **Animal Data:** Testosterone has been tested by subcutaneous injection and implantation in mice
548 and rats. The implant induced cervical-uterine tumors in mice, which metastasized in some cases.
549 There is suggestive evidence that injection of testosterone into some strains of female mice
550 increases their susceptibility to hepatoma. Testosterone is also known to increase the number of
551 tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in
552 rats.

553

554 **Human Data:** There are rare reports of hepatocellular carcinoma in patients receiving long-term
555 therapy with androgens in high doses. Withdrawal of the drugs did not lead to regression of the
556 tumors in all cases.

557

558 Geriatric patients treated with androgens may be at increased risk for the development of
559 prostatic hypertrophy and prostatic carcinoma.

560

561 **Pregnancy (Estrogens)**

562 **ESTRATEST and ESTRATEST H.S.** Tablets should not be used during pregnancy. (See
563 **CONTRAINDICATIONS**.)

564

565 **Pregnancy (Androgens)**

566 *Teratogenic Effects:* Pregnancy Category X. (See **CONTRAINDICATIONS.**)

567

568 **Nursing Mothers (Estrogens)**

569 Estrogen administration to nursing mothers has been shown to decrease the quantity and quality
570 of the milk. Detectable amounts of estrogens have been identified in the milk of mothers
571 receiving this drug. Caution should be exercised when ESTRATEST and ESTRATEST H.S.
572 Tablets are administered to a nursing woman.

573

574 **Nursing Mothers (Androgens)**

575 It is not known whether androgens are excreted in human milk. Because many drugs are excreted
576 in human milk and because of the potential for serious adverse reactions in nursing infants from
577 androgens, a decision should be made whether to discontinue nursing or to discontinue the drug,
578 taking into account the importance of the drug to the mother.

579

580 **Pediatric Use**

581 ESTRATEST and ESTRATEST H.S. Tablets are not indicated for use in children.

582

583 **Geriatric Use**

584 Clinical studies of ESTRATEST and ESTRATEST H.S. Tablets did not include sufficient numbers
585 of subjects aged 65 and over to determine whether they respond differently from younger subjects.
586 Other reported clinical experience has not identified differences in responses between the elderly
587 and younger patients. In general, dose selection for an elderly patient should be cautious, usually
588 starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic,
589 renal, or cardiac function, and of concomitant disease or other drug therapy.

590

591 In the Women's Health Initiative Memory Study, including 4,532 women 65 years of age and
592 older, followed for an average of 4 years, 82% (n = 3,729) were 65 to 74 while 18% (n = 803)
593 were 75 and over. Most women (80%) had no prior hormone therapy use. Women treated with
594 conjugated estrogens plus medroxyprogesterone acetate were reported to have a two-fold
595 increase in the risk of developing probable dementia. Alzheimer's disease was the most common
596 classification of probable dementia in both the conjugated estrogens plus medroxyprogesterone
597 acetate group and the placebo group. Ninety percent of the cases of probable dementia occurred
598 in the 54% of women that were older than 70. (See **WARNINGS, Dementia.**)

599

600 The estrogen alone substudy of the Women's Health Initiative Memory Study has concluded.
601 It is unknown whether these findings apply to estrogen alone.

602

603 **ADVERSE REACTIONS**

604 See **BOXED WARNINGS, WARNINGS and PRECAUTIONS.**

605

606 Because clinical trials are conducted under widely varying conditions, adverse reaction rates
607 observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of
608 another drug and may not reflect the rates observed in practice. The adverse reaction information

609 from clinical trials does, however, provide a basis for identifying the adverse events that appear to
610 be related to drug use and for approximating rates.

611

612 **Associated with Estrogens**

613 (See **WARNINGS** regarding induction of neoplasia, adverse effects on the fetus, increased
614 incidence of gallbladder disease, and adverse effects similar to those of oral contraceptives,
615 including thromboembolism). The following additional adverse reactions have been reported with
616 estrogen and/or progestin therapy.

617

618 **Genitourinary System:** Changes in vaginal bleeding pattern and abnormal withdrawal bleeding
619 or flow; breakthrough bleeding; spotting; dysmenorrhea, increase in size of uterine leiomyomata;
620 vaginitis, including vaginal candidiasis; change in amount of cervical secretion; changes in
621 cervical ectropion; ovarian cancer; endometrial hyperplasia; endometrial cancer; cystitis-like
622 syndrome.

623

624 **Breasts:** Tenderness; enlargement; pain, nipple discharge, galactorrhea; fibrocystic breast changes;
625 breast cancer.

626

627 **Cardiovascular:** Deep and superficial venous thrombosis; pulmonary embolism;
628 thrombophlebitis; myocardial infarction; stroke; increase in blood pressure.

629

630 **Gastrointestinal:** Nausea; vomiting; abdominal cramps; bloating; cholestatic jaundice; increased
631 incidence of gallbladder disease; pancreatitis, enlargement of hepatic hemangiomas.

632

633 **Skin:** Chloasma or melasma that may persist when drug is discontinued; erythema multiforme;
634 erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; pruritus, rash.

635

636 **Eyes:** Retinal vascular thrombosis, steepening of corneal curvature, intolerance to contact lenses.

637

638 **Central Nervous System:** Headache, migraine, dizziness; mental depression; chorea;
639 nervousness; mood disturbances; irritability; exacerbation of epilepsy, dementia.

640

641 **Miscellaneous:** Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of
642 porphyria; edema; arthralgias; leg cramps; changes in libido; urticaria, angioedema,
643 anaphylactoid/anaphylactic reactions; hypocalcemia; exacerbation of asthma; increased
644 triglycerides.

645

646 **Associated with Methyltestosterone**

647 **Endocrine and Urogenital**

648 **Female:** The most common side effects of androgen therapy are amenorrhea and other menstrual
649 irregularities, inhibition of gonadotropin secretion, and virilization, including deepening of the
650 voice and clitoral enlargement. The latter usually is not reversible after androgens are discontinued.

651 When administered to a pregnant woman, androgens cause virilization of external genitalia of the
652 female fetus.

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Skin and Appendages: Hirsutism, male pattern of baldness, and acne.

Fluid and Electrolyte Disturbances: Retention of sodium, chloride, water, potassium, calcium, and inorganic phosphates.

Gastrointestinal: Nausea, cholestatic jaundice, alterations in liver function test, rarely hepatocellular neoplasms, and peliosis hepatis. (See **WARNINGS**.)

Hematologic: Suppression of clotting factors II, V, VII, and X, bleeding in patients on concomitant anticoagulant therapy, and polycythemia.

Central Nervous System: Increased or decreased libido, headache, anxiety, depression, and generalized paresthesia.

Metabolic: Increased serum cholesterol.

Miscellaneous: Inflammation and pain at the site of intramuscular injection or subcutaneous implantation of testosterone containing pellets, stomatitis with buccal preparations, and rarely anaphylactoid reactions.

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing drug products by young children. Overdosage of estrogen may cause nausea and vomiting, and withdrawal bleeding may occur in females.

There have been no reports of acute overdosage with the androgens.

DOSAGE AND ADMINISTRATION

When estrogen is prescribed for a postmenopausal woman with a uterus, a progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin. Use of estrogen, alone or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be reevaluated periodically as clinically appropriate (e.g., 3-month to 6-month intervals) to determine if treatment is still necessary. (See **BOXED WARNINGS** and **WARNINGS**.) For women who have a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

Given cyclically for short-term use only:

For treatment of moderate to severe vasomotor symptoms associated with the menopause in patients not improved by estrogen alone.

696 The lowest dose that will control symptoms should be chosen and medication should be
 697 discontinued as promptly as possible.

698
 699 Administration should be cyclic (e.g., three weeks on and one week off). Attempts to
 700 discontinue or taper medication should be made at three- to six-month intervals.

701

702 ***Usual Dosage Range:***

703 1 tablet of ESTRATEST or 1 to 2 tablets of ESTRATEST H.S. daily as recommended by the
 704 physician.

705

706 Treated patients with an intact uterus should be monitored closely for signs of endometrial
 707 cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of
 708 persistent or recurring abnormal vaginal bleeding.

709

710 **HOW SUPPLIED**

711 ESTRATEST Tablets (Imprinted "SOLVAY 1026")

712 Bottles of 100.....NDC 0032-1026-01

713 Bottles of 1000.....NDC 0032-1026-10

714

715 ESTRATEST Tablets (dark green, capsule shaped, sugar-coated oral tablets) contains: 1.25 mg of
 716 Esterified Estrogens, USP and 2.5 mg of Methyltestosterone, USP.

717

718 ESTRATEST H.S. Tablets (Imprinted "SOLVAY 1023")

719 Bottles of 100.....NDC 0032-1023-01

720

721 ESTRATEST H.S. "Half-Strength" Tablets (light green, capsule shaped, sugar-coated oral tablets)
 722 contains: 0.625 mg of Esterified Estrogens, USP and 1.25 mg of Methyltestosterone, USP.

723

724 **Keep ESTRATEST and ESTRATEST H.S. Tablets out of reach of children.**

725

726 **Store at controlled room temperature 15° to 30°C (59° to 86°F).**

727

728 ‡ This product has not obtained FDA pre-market approval applicable for new drugs.

729

730

PATIENT INFORMATION

(Updated 09 Jan 2005)

ESTRATEST®‡ and ESTRATEST® H.S.‡
(Esterified Estrogens and Methyltestosterone) Tablets

R_x only

Read this PATIENT INFORMATION before you start taking ESTRATEST® and ESTRATEST® H.S. Tablets and read what you get each time you refill ESTRATEST and ESTRATEST H.S. Tablets. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

**WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT
ESTRATEST AND ESTRATEST H.S. TABLETS
(A COMBINATION OF ESTROGEN AND ANDROGEN HORMONES)?**

- Estrogens increase the chances of getting cancer of the uterus.

Report any unusual vaginal bleeding right away while you are taking estrogens. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.

- Do not use estrogens with or without progestins to prevent heart disease, heart attacks, or strokes.

Using estrogens with or without progestins may increase your chances of getting heart attacks, strokes, breast cancer, and blood clots. Using estrogens with progestins may increase your risk of dementia. You and your healthcare provider should talk regularly about whether you still need treatment with ESTRATEST and ESTRATEST H.S. Tablets.

What is ESTRATEST and ESTRATEST H.S. Tablets?

ESTRATEST and ESTRATEST H.S. Tablets are medicines that contain estrogen and androgen hormones.

What is ESTRATEST and ESTRATEST H.S. Tablets used for?

ESTRATEST and ESTRATEST H.S. Tablets are used after menopause to:

- **reduce moderate to severe hot flashes.** Estrogens are hormones made by a woman's ovaries. The ovaries normally stop making estrogens when a woman is between 45 to 55 years old. This drop in body estrogen levels causes the "change of life" or menopause (the end of monthly menstrual periods). Sometimes, both ovaries are removed during an

754 operation before natural menopause takes place. The sudden drop in estrogen levels causes
755 “surgical menopause.”
756

757 When the estrogen levels begin dropping, some women develop very uncomfortable
758 symptoms, such as feelings of warmth in the face, neck, and chest, or sudden strong feelings
759 of heat and sweating (“hot flashes” or “hot flushes”). In some women, the symptoms are
760 mild, and they will not need estrogens. In other women, symptoms can be more severe. You
761 and your healthcare provider should talk regularly about whether you still need treatment
762 with ESTRATEST and ESTRATEST H.S. Tablets.
763

764 • **treat moderate to severe dryness, itching, and burning in and around the vagina.** You
765 and your healthcare provider should talk regularly about whether you still need treatment
766 with ESTRATEST and ESTRATEST H.S. Tablets to control these problems. If you use
767 ESTRATEST and ESTRATEST H.S. Tablets only to treat your dryness, itching, and burning
768 in and around your vagina, talk with your healthcare provider about whether a topical vaginal
769 product would be better for you.
770

771 **Who should not take ESTRATEST and ESTRATEST H.S. Tablets?**

772 Do not start taking ESTRATEST or ESTRATEST H.S. Tablets if you:

- 773 • **have unusual vaginal bleeding.**
- 774 • **currently have or have had certain cancers.** Estrogens may increase the chances of getting
775 certain types of cancers, including cancer of the breast or uterus. If you have or had cancer,
776 talk with your healthcare provider about whether you should take ESTRATEST or
777 ESTRATEST H.S. Tablets.
- 778 • **had a stroke or heart attack in the past year.**
- 779 • **currently have or have had blood clots.**
- 780 • **currently have or have had liver problems.**
- 781 • **are allergic to ESTRATEST or ESTRATEST H.S. Tablets or any of their ingredients.**
782 See the end of this leaflet for a list of ingredients in ESTRATEST and ESTRATEST H.S.
783 Tablets.
- 784 • **think you may be pregnant.**
785

786 **Tell your healthcare provider:**

- 787 • **if you are breastfeeding.** The hormones in ESTRATEST and ESTRATEST H.S. Tablets
788 can pass into your milk.
- 789 • **about all of your medical problems.** Your healthcare provider may need to check you more
790 carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures),
791 migraine, endometriosis, lupus, problems with your heart, liver, thyroid, kidneys, or have
792 high calcium levels in your blood.
- 793 • **about all the medicines you take.** This includes prescription and nonprescription
794 medicines, vitamins, and herbal supplements. Some medicines may affect how ESTRATEST
795 and ESTRATEST H.S. Tablets work. ESTRATEST and ESTRATEST H.S. Tablets may
796 also affect how your other medicines work.
- 797 • **if you are going to have surgery or will be on bed rest.** You may need to stop taking
798 estrogens.

799

800 How should I take ESTRATEST and ESTRATEST H.S. Tablets?

801 Estrogens should be used at the lowest dose possible for your treatment only as long as needed.
802 The lowest effective dose of ESTRATEST and ESTRATEST H.S. Tablets has not been
803 determined. You and your healthcare provider should talk regularly (for example, every 3 to 6
804 months) about the dose you are taking and whether you still need treatment with ESTRATEST
805 and ESTRATEST H.S. Tablets.

806

807 What are the possible side effects of estrogens?**808 Less common but serious side effects include:**

- 809 • Breast cancer
- 810 • Cancer of the uterus
- 811 • Stroke
- 812 • Heart attack
- 813 • Blood clots
- 814 • Dementia
- 815 • Gallbladder disease
- 816 • Ovarian cancer

817

818 These are some of the warning signs of serious side effects:

- 819 • Breast lumps
- 820 • Unusual vaginal bleeding
- 821 • Dizziness and faintness
- 822 • Changes in speech
- 823 • Severe headaches
- 824 • Chest pain
- 825 • Shortness of breath
- 826 • Pains in your legs
- 827 • Changes in vision
- 828 • Vomiting

829

830 Call your healthcare provider right away if you get any of these warning signs, or any other
831 unusual symptom that concerns you.

832

833 Common side effects include:

- 834 • Headache
- 835 • Breast pain
- 836 • Irregular vaginal bleeding or spotting
- 837 • Stomach/abdominal cramps, bloating
- 838 • Nausea and vomiting
- 839 • Hair loss

840

841 Other side effects include:

- 842 • High blood pressure

- 843 • Liver problems
- 844 • High blood sugar
- 845 • Fluid retention
- 846 • Enlargement of benign tumors of the uterus (“fibroids”)
- 847 • Vaginal yeast infection

848

849 These are not all the possible side effects of ESTRATEST and ESTRATEST H.S. Tablets. For
850 more information, ask your healthcare provider or pharmacist.

851

852 **What can I do to lower my chance of a serious side effect with ESTRATEST and** 853 **ESTRATEST H.S. Tablets?**

- 854 • Talk with your healthcare provider regularly about whether you should continue taking
855 ESTRATEST and ESTRATEST H.S. Tablets.
- 856 • If you have a uterus, talk to your healthcare provider about whether the addition of a
857 progestin is right for you.
- 858 • See your healthcare provider right away if you get vaginal bleeding while taking
859 ESTRATEST and ESTRATEST H.S. Tablets.
- 860 • Have a breast exam and mammogram (breast X-ray) every year unless your healthcare
861 provider tells you something else. If members of your family have had breast cancer or if you
862 have ever had breast lumps or an abnormal mammogram, you may need to have breast exams
863 more often.
- 864 • If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight,
865 or if you use tobacco, you may have higher chances for getting heart disease. Ask your
866 healthcare provider for ways to lower your chances for getting heart disease.

867

868 **General information about safe and effective use of ESTRATEST and ESTRATEST** 869 **H.S. Tablets**

870 Medicines are sometimes prescribed for conditions that are not mentioned in patient information
871 leaflets. Do not take ESTRATEST and ESTRATEST H.S. Tablets for conditions for which it
872 was not prescribed. Do not give ESTRATEST and ESTRATEST H.S. Tablets to other people,
873 even if they have the same symptoms you have. It may harm them.

874

875 **Keep ESTRATEST and ESTRATEST H.S. Tablets out of the reach of children.**

876

877 This leaflet provides a summary of the most important information about ESTRATEST and
878 ESTRATEST H.S. Tablets. If you would like more information, talk with your healthcare
879 provider or pharmacist. You can ask for information about ESTRATEST and ESTRATEST H.S.
880 Tablets that is written for health professionals. You can get more information by calling the toll
881 free number 1-800-241-1643.

882

883 **What are the ingredients in ESTRATEST and ESTRATEST H.S. Tablets?**

884 ESTRATEST H.S. is a combination of Esterified Estrogens and Methyltestosterone. Each capsule-
885 shaped, light green, sugar-coated tablet contains the following active ingredients: 0.625 mg of
886 Esterified Estrogens, USP and 1.25 mg of Methyltestosterone, USP.

887
888 ESTRATEST is a combination of Esterified Estrogens and Methyltestosterone. Each capsule-
889 shaped, dark green, sugar-coated tablet contains the following active ingredients: 1.25 mg of
890 Esterified Estrogens, USP and 2.5 mg of Methyltestosterone, USP.

891
892 ESTRATEST and ESTRATEST H.S. Tablets contain the following inactive ingredients:
893 acacia, acetylated monoglycerides, calcium carbonate, carboxymethylcellulose sodium, carnauba
894 wax NF, citric acid, colloidal silicon dioxide, gelatin, iron oxide, lactose, magnesium stearate,
895 methylparaben, microcrystalline cellulose, pharmaceutical glaze, povidone, propylene glycol,
896 propylparaben, shellac glaze, sodium benzoate, sodium bicarbonate, sorbic acid, starch, sucrose,
897 talc, titanium dioxide, and tribasic calcium phosphate.

898
899 ESTRATEST Tablets also include: FD&C Blue No. 1 Lake, FD&C Yellow No. 6 Lake, and
900 D&C Yellow No. 10 Lake.

901
902 ESTRATEST H.S. Tablets also include: D&C Yellow No. 10 Lake, FD&C Blue No. 1 Lake,
903 FD&C Blue No. 2 Lake, FD&C Yellow No. 6 Lake, and FD&C Red No. 40 Lake.

904
905 **Store at controlled room temperature 15° to 30°C (59° to 86°F).**

906
907
908 ‡ This product has not obtained FDA pre-market approval applicable for new drugs.

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911 500160
912 Rev Jan 2005

913
914 **Solvay**
915 **Pharmaceuticals, Inc.**
916 Marietta, GA 30062

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919