

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-102**

**APPROVED LABELING**

1

ITEM 2.3.1.1.

2

3

4

5

APPEARS THIS WAY  
ON ORIGINAL

6

7

8

9

*femhrt 1/5*

10

*femhrt* US Draft Labeling Physician Package Insert

APPEARS THIS WAY  
ON ORIGINAL

|    |                                                      |                                     |
|----|------------------------------------------------------|-------------------------------------|
| 11 | DESCRIPTION                                          | 3                                   |
| 12 | CLINICAL PHARMACOLOGY                                | 3                                   |
| 13 | Mechanism of Action                                  | <b>Error! Bookmark not defined.</b> |
| 14 | Pharmacokinetics                                     | 4                                   |
| 15 | Absorption and Bioavailability                       | 4                                   |
| 16 | Distribution                                         | 7                                   |
| 17 | Metabolism                                           | 7                                   |
| 18 | Excretion                                            | 8                                   |
| 19 | Special Populations                                  | 8                                   |
| 20 | Patients With Hepatic Impairment                     | 9                                   |
| 21 | Geriatrics                                           | 8                                   |
| 22 | Race                                                 | 8                                   |
| 23 | Drug Interactions                                    | 9                                   |
| 24 | Clinical Studies                                     | 9                                   |
| 25 | INDICATIONS AND USAGE                                | 14                                  |
| 26 | CONTRAINDICATIONS                                    | 15                                  |
| 27 | WARNINGS                                             | 15                                  |
| 28 | PRECAUTIONS                                          | 17                                  |
| 29 | General                                              | 17                                  |
| 30 | Information for Patients                             | 20                                  |
| 31 | Drug Interactions                                    | 20                                  |
| 32 | Carcinogenesis, Mutagenesis, Impairment of Fertility | 22                                  |
| 33 | Pregnancy Category X                                 | 22                                  |
| 34 | Nursing Mothers                                      | 22                                  |
| 35 | ADVERSE REACTIONS                                    | 22                                  |
| 36 | Clinical Adverse Experience                          | <b>Error! Bookmark not defined.</b> |
| 37 | ACUTE OVERDOSAGE                                     | 24                                  |
| 38 | DOSAGE AND ADMINISTRATION                            | 24                                  |
| 39 | HOW SUPPLIED                                         | 25                                  |

40

41 **femhrt (norethindrone acetate/ethinyl estradiol tablets)**

42

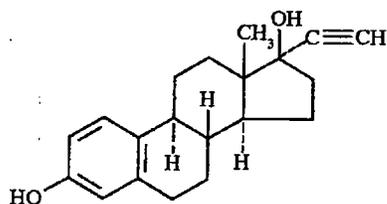
43 **DESCRIPTION**

44

45 *femhrt* 1/5 is a continuous dosage regimen of a progestin-estrogen combination for oral  
46 administration.

47 Each white D-shaped tablet contains 1 mg norethindrone acetate [(17- $\alpha$ )-17-  
48 (acetyloxy)-19-norpregna-4-en-20-yn-3-one] and 5 mcg ethinyl estradiol [(17- $\alpha$ )-19-  
49 norpregna-1,3,5(10)-trien-20-yn-2,17-diol]. Each tablet also contains calcium stearate,  
50 lactose monohydrate, microcrystalline cellulose, and corn starch.

51 The structural formulas are as follows:



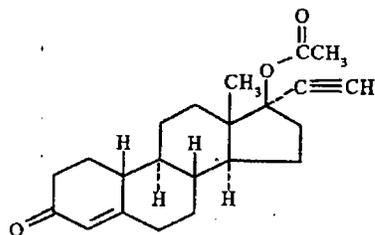
52

53 Ethinyl Estradiol

54 Molecular Weight: 296.41

55 Molecular Formula: C<sub>20</sub>H<sub>24</sub>O<sub>2</sub>

APPEARS THIS WAY  
ON ORIGINAL



56

57 Norethindrone Acetate

58 Molecular Weight: 340.47

59 Molecular Formula: C<sub>22</sub>H<sub>28</sub>O<sub>3</sub>

60

61 **CLINICAL PHARMACOLOGY**

62 Estrogens are largely responsible for the development and maintenance of the female  
63 reproductive system and secondary sex characteristics. Although circulating estrogens  
64 exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal

65 intracellular human estrogen and is substantially more potent than estrone and estriol at  
66 the receptor level. The primary source of estrogen in normally cycling adult women is the  
67 ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase  
68 of the menstrual cycle. After menopause, most endogenous estrogen is produced by  
69 conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral  
70 tissues. Thus, estrone and the sulphate conjugated form, estrone sulphate, are the most  
71 abundant circulating estrogens in postmenopausal women. The pharmacologic effects of  
72 ethinyl estradiol are similar to those of endogenous estrogens.

73 Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing  
74 hormone (LH) and follicle stimulating hormone (FSH) through a negative feedback  
75 mechanism. Estrogen replacement therapy acts to reduce the elevated levels of these  
76 hormones seen in postmenopausal women.

77 Progestin compounds enhance cellular differentiation and generally oppose the actions of  
78 estrogens by decreasing estrogen receptor levels, increasing local metabolism of estrogens  
79 to less active metabolites, or inducing gene products that blunt cellular responses to  
80 estrogen. Progestins exert their effects in target cells by binding to specific progesterone  
81 receptors that interact with progesterone response elements in target genes. Progesterone  
82 receptors have been identified in the female reproductive tract, breast, pituitary,  
83 hypothalamus, bone, skeletal tissue and central nervous system. Progestins produce  
84 similar endometrial changes to those of the naturally occurring hormone progesterone.

85 The use of unopposed estrogen therapy has been associated with an increased risk of  
86 endometrial hyperplasia, a possible precursor of endometrial adenocarcinoma. The  
87 addition of continuous administration of progestin to an estrogen replacement regimen  
88 reduced the incidence of endometrial hyperplasia, and the attendant risk of carcinoma in  
89 women with intact uteri.

## 90 **Pharmacokinetics**

### 91 **Absorption and Bioavailability**

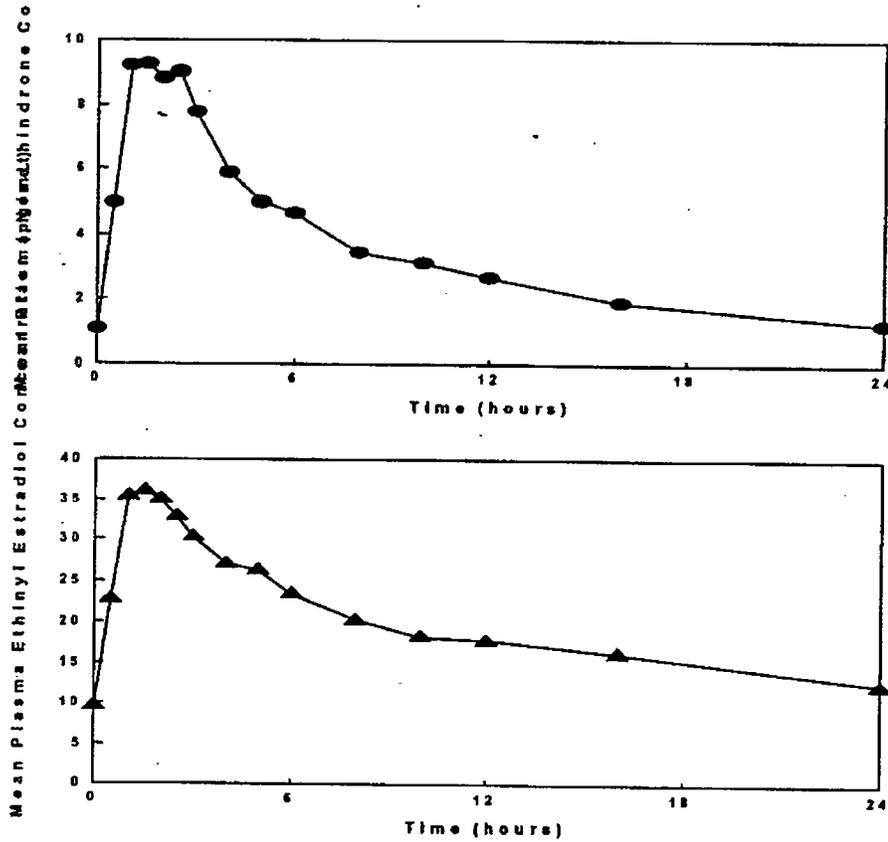
92 Norethindrone acetate (NA) is completely and rapidly deacetylated to norethindrone after  
93 oral administration, and the disposition of norethindrone acetate is indistinguishable from  
94 that of orally administered norethindrone. Norethindrone acetate and ethinyl estradiol  
95 (EE) are rapidly absorbed from *femhrt* 1/5 tablets, with maximum plasma concentrations  
96 of norethindrone and ethinyl estradiol generally occurring 1 to 2 hours postdose. Both are

97 subject to first-pass metabolism after oral dosing, resulting in an absolute bioavailability  
98 of approximately 64% for norethindrone and 55% for ethinyl estradiol. Bioavailability of  
99 *femhrt* 1/5 tablets is similar to that from solution for norethindrone and slightly less for  
100 ethinyl estradiol. Administration of norethindrone acetate/ethinyl estradiol (NA/EE)  
101 tablets with a high fat meal decreases rate but not extent of ethinyl estradiol absorption.  
102 The extent of norethindrone absorption is increased by 27% following administration of  
103 NA/EE tablets with food.

104 The full pharmacokinetic profile of *femhrt* 1/5 (1 mg norethindrone acetate/5 mcg ethinyl  
105 estradiol) was not characterized due to assay sensitivity limitations. However, the  
106 multiple-dose pharmacokinetics were studied at a dose of 1 mg NA/10 mcg EE in 18  
107 post-menopausal women. Mean plasma concentrations are shown below (Figure 1) and  
108 pharmacokinetic parameters are found in Table 1. Based on a population  
109 pharmacokinetic analysis, mean steady state concentrations of norethindrone for 1 mg  
110 NA/5 mcg EE and 1/10 are slightly more than proportional to dose when compared to 0.5  
111 mg NA/2.5 mcg EE tablets. It can be explained by higher sex hormone binding globulin  
112 (SHBG) concentrations. Mean steady-state plasma concentrations of ethinyl estradiol for  
113 the 0.5 mg NA/2.5 mcg EE tablets and *femhrt* 1/5 tablets are proportional to dose, but  
114 there is a less than proportional increase in steady state concentrations for the NA/EE  
115 1/10 tablet.

APPEARS THIS WAY  
ON ORIGINAL

116 **Figure 1. Mean Steady-State (Day 87) Plasma Norethindrone and Ethinyl**  
117 **Estradiol Concentrations Following Continuous Oral Administration of 1mg NA/10**  
118 **mcg EE Tablets**



119

APPEARS THIS WAY  
ON ORIGINAL

120

**Table 1. Mean (SD) Single-Dose (Day 1) and Steady-State (Day 87) Pharmacokinetic Parameters<sup>a</sup> Following Administration of 1 mg NA/10 mcg EE Tablets**

|                          | C <sub>max</sub><br>ng/mL | t <sub>max</sub><br>hr | AUC(0-24)<br>ng-hr/mL | CL/F<br>mL/min  | t <sub>1/2</sub><br>hr |
|--------------------------|---------------------------|------------------------|-----------------------|-----------------|------------------------|
| <b>NORETHINDRONE</b>     |                           |                        |                       |                 |                        |
| Day 1                    | 6.0 (3.3)                 | 1.8 (0.8)              | 29.7 (16.5)           | 588 (416)       | 10.3 (3.7)             |
| Day 87                   | 10.7 (3.6)                | 1.8 (0.8)              | 81.8 (36.7)           | 226 (139)       | 13.3 (4.5)             |
| <b>ETHINYL ESTRADIOL</b> | pg/mL                     | hr                     | pg-hr/mL              | mL/min          | hr                     |
| Day 1                    | 33.5 (13.7)               | 2.2 (1.0)              | 339 (113)             | ND <sup>b</sup> | ND <sup>b</sup>        |
| Day 87                   | 38.3 (11.9)               | 1.8 (0.7)              | 471 (132)             | 383 (119)       | 23.9 (7.1)             |

<sup>a</sup> C<sub>max</sub> = Maximum plasma concentration; t<sub>max</sub> = time of C<sub>max</sub>; AUC(0-24) = Area under the plasma concentration-time curve over the dosing interval; and CL/F = Apparent oral clearance; t<sub>1/2</sub> = Elimination half-life; <sup>b</sup>ND=Not determined

121

122 Based on a population pharmacokinetic analysis, average steady-state concentrations  
123 (C<sub>ss</sub>) of norethindrone and ethinyl estradiol for *femhrt* 1/5 (1 mg NA/5 mcg EE) tablets  
124 are estimated to be 2.6 ng/mL and 11.4 pg/mL, respectively.

125 The pharmacokinetics of ethinyl estradiol and norethindrone acetate were not affected by  
126 age, (age range 40-62 years), in the postmenopausal population studied.

127 **Distribution**

128

129 Volume of distribution of norethindrone and ethinyl estradiol ranges from 2 to 4 L/kg.  
130 Plasma protein binding of both steroids is extensive (>95%); norethindrone binds to both  
131 albumin and sex hormone binding globulin (SHBG), whereas ethinyl estradiol binds only  
132 to albumin. Although ethinyl estradiol does not bind to SHBG, it induces SHBG  
133 synthesis.

134

135 **Metabolism**

136 Norethindrone undergoes extensive biotransformation, primarily via reduction, followed  
137 by sulfate and glucuronide conjugation. The majority of metabolites in the circulation are  
138 sulfates, with glucuronides accounting for most of the urinary metabolites. A small  
139 amount of norethindrone acetate is metabolically converted to ethinyl estradiol, such that  
140 exposure to ethinyl estradiol following administration of 1 mg of norethindrone acetate is  
141 equivalent to oral administration of 2.8 mcg ethinyl estradiol. Ethinyl estradiol is also  
142 extensively metabolized, both by oxidation and by conjugation with sulfate and  
143 glucuronide. Sulfates are the major circulating conjugates of ethinyl estradiol and

144 glucuronides predominate in urine. The primary oxidative metabolite is 2-hydroxy  
145 ethinyl estradiol, formed by the CYP3A4 isoform of cytochrome P450. Part of the first-  
146 pass metabolism of ethinyl estradiol is believed to occur in gastrointestinal mucosa.  
147 Ethinyl estradiol may undergo enterohepatic circulation.

148 **Excretion**

149 Norethindrone and ethinyl estradiol are excreted in both urine and feces, primarily as  
150 metabolites. Plasma clearance values for norethindrone and ethinyl estradiol are similar  
151 (approximately 0.4 L/hr/kg). Steady-state elimination half-lives of norethindrone and  
152 ethinyl estradiol following administration of 1 mg NA/10 mcg EE tablets are  
153 approximately 13 hours and 24 hours, respectively.

154 **Special Populations**

155 **Pediatric**

156

157 *femhrt* 1/5 is not indicated in children.

158

159 **Geriatrics**

160 The pharmacokinetics of *femhrt* 1/5 have not been studied in a geriatric population.

161 **Race**

162 The effect of race on the pharmacokinetics of *femhrt* 1/5 has not been studied.

163

164 **Patients with Renal Insufficiency**

165 The effect of renal disease on the disposition of *femhrt* 1/5 has not been evaluated. In  
166 premenopausal women with chronic renal failure undergoing peritoneal dialysis who  
167 received multiple doses of an oral contraceptive containing ethinyl estradiol and  
168 norethindrone, plasma ethinyl estradiol concentrations were higher and norethindrone  
169 concentrations were unchanged compared to concentrations in premenopausal women  
170 with normal renal function (see **Precautions: Fluid Retention**).

171 **Patients with Hepatic Impairment**

172 The effect of hepatic disease on the disposition of *femhrt* 1/5 has not been evaluated.  
173 However, ethinyl estradiol and norethindrone may be poorly metabolized in patients with  
174 impaired liver function (see **Precautions**).

175 **Drug Interactions**

176 See **PRECAUTIONS, Drug Interactions**.

177 **Clinical Studies**

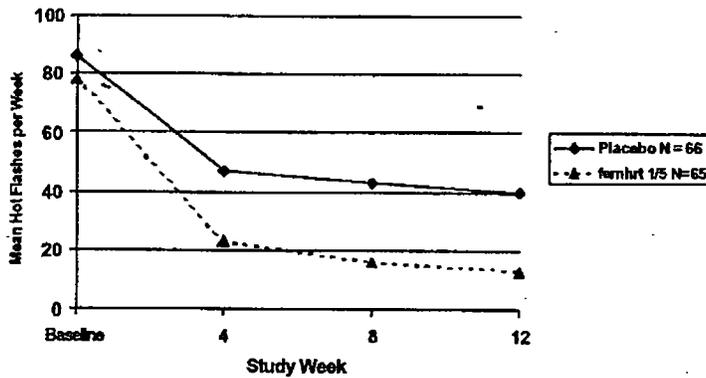
178 **Effects on Vasomotor Symptoms**

179  
180 A 12-week placebo-controlled, multicenter, randomized clinical trial was conducted to  
181 determine the safety and efficacy of *femhrt* 1/5 for the treatment of vasomotor symptoms.  
182 The study assessed the efficacy of *femhrt* 1/5 in 266 symptomatic women who had at  
183 least 56 moderate to severe hot flashes during the week prior to randomization. On  
184 average, these patients had 12 hot flashes per day upon study entry.

185 The efficacy of *femhrt* 1/5 for the treatment of moderate to severe vasomotor symptoms  
186 (VMS) is demonstrated in Figure 2.

APPEARS THIS WAY  
ON ORIGINAL

Figure 2: Mean Hot Flash Frequencies by Treatment Group:  
Baseline Through Week 12 (Intent to Treat population, Last  
observation carried forward)



187

188 **Endometrial Hyperplasia**

189 A 2-year, placebo-controlled, multicenter, randomized clinical trial was conducted to  
190 determine the safety and efficacy of *femhrt* 1/5 on maintaining bone mineral density,  
191 protecting the endometrium, and to determine effects on lipids. A total of 1265 women  
192 were enrolled and randomized to either placebo, 0.2 mg NA/1 mcg EE, 0.5 mg NA/2.5  
193 mcg EE, *femhrt* 1/5 and 1 mg NA/10 mcg EE or matching unopposed EE doses (1, 2.5,  
194 5, or 10 mcg) for a total of 9 treatment groups. All participants received 1000 mg of  
195 calcium supplementation daily. Of the 1265 women randomized to the various treatment  
196 arms of this study, 137 were randomized to placebo, 146 to *femhrt* 1/5, and 141 to EE 5  
197 mcg. Of these, 134 placebo, 143 *femhrt* 1/5, and 139 EE 5 mcg had a baseline  
198 endometrial result. Baseline biopsies were classified as normal (in approximately 95% of  
199 subjects), or insufficient tissue (in approximately 5% of subjects). Follow-up biopsies  
200 were obtained in approximately 70-80% of patients in each arm after 12 and 24 months  
201 of therapy. Results are shown in Table 2.

202

203

APPEARS THIS WAY  
ON ORIGINAL

204 **Table 2. Endometrial Biopsy Results After 12 and 24 Months of Treatment**

| Number of Patients Biopsied at Baseline | Placebo<br>N= 134 | femhrt 1/5<br>N= 143 | 5 mcg ethinyl estradiol<br>N=139 |
|-----------------------------------------|-------------------|----------------------|----------------------------------|
| <b>MONTH 12</b>                         |                   |                      |                                  |
| Patients Biopsied (%)                   | 113 (84)          | 110 (77)             | 114 (82)                         |
| Insufficient Tissue                     | 30                | 45                   | 20                               |
| Atrophic Tissue                         | 60                | 41                   | 2                                |
| Proliferative Tissue                    | 23                | 24                   | 91                               |
| Endometrial Hyperplasia <sup>a</sup>    | 0                 | 0                    | 1                                |
| <b>MONTH 24</b>                         |                   |                      |                                  |
| Patients Biopsied (%)                   | 94 (70)           | 102 (71)             | 107 (77)                         |
| Insufficient Tissue                     | 35                | 37                   | 17                               |
| Atrophic Tissue                         | 38                | 33                   | 2                                |
| Proliferative Tissue                    | 20                | 32                   | 86                               |
| Endometrial Hyperplasia <sup>a</sup>    | 1                 | 0                    | 2                                |

205  
206  
207  
208  
209  
210  
211  
212  
213

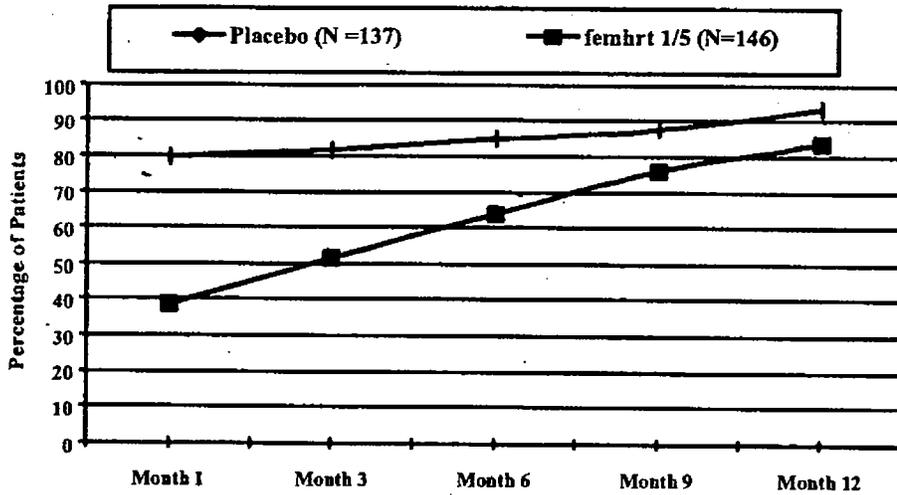
<sup>a</sup>All patients with endometrial hyperplasia were carried forward for all time points

**Irregular Bleeding/Spotting**

The cumulative incidence of amenorrhea, defined as no bleeding or spotting, was evaluated over 12 months for femhrt 1/5 and placebo arms. Results are shown in Figure 3.

APPEARS THIS WAY  
ON ORIGINAL

214 **Figure 3. Patients with Cumulative Amenorrhea Over Time: Intent-To Treat**  
215 **Population, Last Observation Carried Forward**



216

217

218 **Effect on Bone Mineral Density**

219

220 In the 2 year study, trabecular bone mineral density (BMD) was assessed at lumbar spine  
221 using quantitative computed tomography. A total of 283 postmenopausal women with  
222 intact uteri and normal baseline bone mineral density ( $124.14 \text{ mg/cc} \pm 9.60 \text{ mg/cc}$ ) were  
223 randomized to *femhrt* 1/5 (1 mg norethindrone acetate/5 mcg ethinyl estradiol) or  
224 placebo, and 87% contributed data to the Intent-To-Treat analysis. All patients received  
225 1000 mg calcium in divided doses. Vitamin D was not supplemented. *femhrt* 1/5  
226 resulted in significant increases in BMD at each assessment. There was a significant  
227 decrease in BMD in the placebo group (see Figure 4).

228

229

230

231

232

233

234

235

236

237

238

239

240

241

242

243

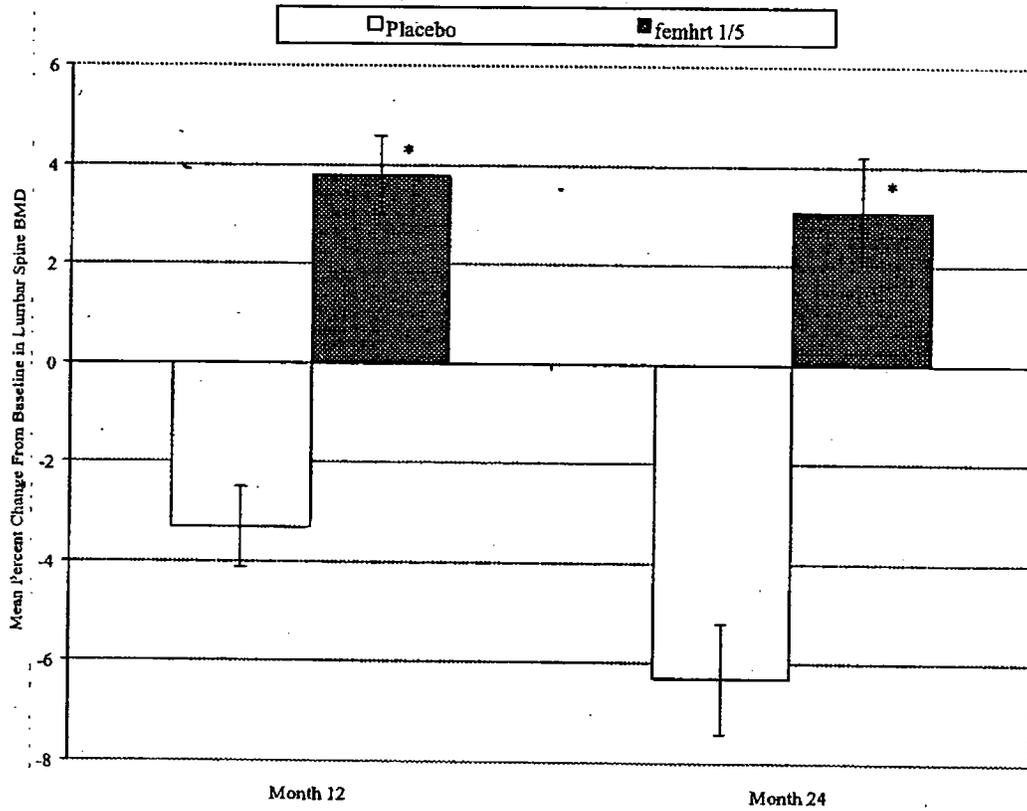
244

245

246

APPEARS THIS WAY  
ON ORIGINAL

247 **Figure 4. Mean Percent Change ( $\pm$  SE) From Baseline in Lumbar Spine BMD at**  
248 **Months 12 and 24 (Intent-to-Treat Population)**  
249



250  
251  
252  
253  
254  
255  
256

\* Mean percent changes in BMD statistically significantly more positive than mean percent changes in placebo group at each time point.

257 **Information Regarding Lipid Effects**

258 Patients enrolled in the 2-year osteoporosis and endometrial protection trial were  
259 evaluated for changes in lipid parameters after 24 months of therapy. All subjects were  
260 postmenopausal women at low risk for cardiovascular disease. Results for *femhrt 1/5* and  
261 placebo arms are shown in Table 3.

262

**Table 3. Mean % Change From Baseline Lipid Profile.  
Values After 24 Months of Treatment**

| Lipid Parameter           | Placebo | femhrt 1/5 (mg<br>NA/mcg EE) |
|---------------------------|---------|------------------------------|
|                           | N = 129 | N = 132                      |
| Total Cholesterol (mg/dL) | 1.6     | -7.0                         |
| HDL-C (mg/dL)             | 1.3     | -6.7                         |
| LDL-C (mg/dL)             | 1.0     | -7.5                         |
| Triglycerides (mg/dL)     | 19.1    | 12.1                         |

NA = Norethindrone acetate. EE = Ethinyl estradiol.

263

## 264 INDICATIONS AND USAGE

265 *femhrt* 1/5 is indicated in women with an intact uterus for the:

- 266 1. Treatment of moderate to severe vasomotor symptoms associated with menopause.
- 267 2. Prevention of osteoporosis.

268

269 Since estrogen administration is associated with risks as well as benefits, selection of  
270 patients ideally should be based on prospective identification of risk factors for  
271 developing osteoporosis. Unfortunately, there is no certain way to identify those women  
272 who will develop osteoporotic fractures. Thus, patient selection must be individualized  
273 based on the balance of risks and benefits.

274 Estrogen replacement therapy reduces bone resorption and retards or halts  
275 postmenopausal bone loss. Case-control studies have shown an approximately 60%  
276 reduction in hip and wrist fractures in women whose estrogen replacement was begun  
277 within a few years of menopause. Studies also suggest that estrogen reduces the rate of  
278 vertebral fractures. Even when started as late as 6 years after menopause, estrogen may  
279 prevent further loss of bone mass for as long as the treatment is continued. When  
280 estrogen therapy is discontinued, bone mass declines at a rate comparable to that in the  
281 immediate postmenopausal period. There is no evidence that estrogen replacement  
282 therapy restores bone mass to premenopausal levels.

283 Early menopause is one of the strongest predictors for the development of osteoporosis.

284 The mainstays of prevention and management of postmenopausal osteoporosis are  
285 estrogen, an adequate lifetime calcium intake, vitamin D and exercise. Postmenopausal  
286 women absorb dietary calcium less efficiently than premenopausal women and require an

287 average of 1500 mg/day of elemental calcium to remain in neutral calcium balance. By  
288 comparison, premenopausal women require about 1000 mg/day and the average calcium  
289 intake in the USA is 400 to 600 mg/day. Therefore, when not contraindicated, calcium  
290 supplementation and adequate daily intake of vitamin D (400 IU) may be helpful.

## 291 **CONTRAINDICATIONS**

292 Progestogens/estrogens should not be used in individuals with any of the following  
293 conditions or circumstances:

- 294 1. Known or suspected pregnancy, including use for missed abortion or as a diagnostic  
295 test for pregnancy. Progestin or estrogen may cause fetal harm when administered to  
296 a pregnant woman.
- 297 2. Known or suspected cancer of the breast.
- 298 3. Known or suspected estrogen-dependent neoplasia.
- 299 4. Undiagnosed abnormal genital bleeding.
- 300 5. Active or past history of thrombophlebitis or thromboembolic disorders.
- 301 6. Known sensitivity to *femhrt* 1/5 or other estrogen and progestin containing products.

## 302 **WARNINGS**

### 303 **1. Induction of malignant neoplasms**

#### 304 **Endometrial Cancer**

305 The reported endometrial cancer risk among users of unopposed estrogen is about 2- to  
306 12-fold greater than in nonusers, and appears dependent on duration of treatment and on  
307 estrogen dose. Most studies show no significant increased risk associated with the use of  
308 estrogens for less than 1 year. The greatest risk appears associated with prolonged use,  
309 with increased risks of 15- to 24-fold for use of 5 to 10 years or more, and this risk has  
310 been shown to persist for at least 15 years after cessation of estrogen treatment. Results  
311 from a 2-year clinical study of the effects of *femhrt* 1/5 on endometrial hyperplasia are  
312 shown in the **Clinical Studies** section of this label.

313 Clinical surveillance of all women taking progestin/estrogen combinations is important.  
314 Adequate diagnostic measures, including endometrial sampling when indicated, should  
315 be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring

316 abnormal vaginal bleeding. There is no evidence that "natural" estrogens are more or  
317 less hazardous than "synthetic" estrogens at equivalent doses.

318 **Breast Cancer**

319 While the majority of studies have not shown an increased risk of breast cancer in women  
320 who have ever used estrogen replacement therapy, some have reported a moderately  
321 increased risk (relative risks of 1.3-2.0) in those taking higher doses or those taking lower  
322 doses for prolonged periods of time, especially in excess of 10 years.

323 The effect of added progestins on the risk of breast cancer is unknown.

324 **2. Gallbladder Disease**

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

327 **3. Hypercalcemia**

328 Administration of estrogens may lead to severe hypercalcemia in patients with breast  
329 cancer and bone metastases (see **Contraindications**). If this occurs, the drugs should be  
330 stopped and appropriate measures taken to reduce the serum calcium level.

331 **4. Pregnancy**

332 Use in pregnancy is not recommended (see **Contraindications**).

333 **5. Venous Thromboembolism**

334 Five epidemiologic studies have found an increased risk of venous thromboembolism  
335 (VTE) in users of estrogen replacement therapy (ERT) who did not have predisposing  
336 conditions for VTE, such as a past history of cardiovascular disease or a recent history of  
337 pregnancy, surgery, trauma, or serious illness. The increased risk was found only in  
338 current ERT users; it did not persist in former users. The risk appeared to be higher in the  
339 first year of use and decreased thereafter. The findings were similar for ERT alone or  
340 with added progestin and pertain to commonly used oral and transdermal doses, with a  
341 possible dose-dependent effect on risk. The studies found the VTE risk to be about one  
342 case per 10,000 women per year among women not using ERT and without predisposing

343 conditions. The risk in current ERT users was increased to 2-3 cases per 10,000 women  
344 per year.

345 **6. Visual Disturbances**

346 Medication should be discontinued pending examination if there is a sudden partial or  
347 complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If  
348 examination reveals papilledema or retinal vascular lesions, medication should be  
349 withdrawn.

350 **PRECAUTIONS**

351 **A. General**

352 Based on experience with estrogens and/or progestins:

353 **1. Cardiovascular Risk**

354 A causal relationship between estrogen replacement therapy and reduction of  
355 cardiovascular disease in postmenopausal women has not been proven. Furthermore, the  
356 effect of added progestins on this putative benefit is not yet known.

357 In recent years many published studies have suggested that there may be a cause-effect  
358 relationship between postmenopausal oral estrogen replacement therapy without cyclical  
359 progestins and a decrease in cardiovascular disease in women. Although most of the  
360 observational studies which assessed this statistical association have reported a 20% to  
361 50% reduction in coronary heart disease risk and associated mortality in estrogen takers,  
362 the following should be considered when interpreting these reports:

363 (1) Because only one of these studies was randomized and it was too small to yield  
364 statistically significant results, all relevant studies were subject to selection bias. Thus,  
365 the apparently reduced risk of coronary artery disease cannot be attributed with certainty  
366 to estrogen replacement therapy. It may instead have been caused by life-style and  
367 medical characteristics of the women studied with the result that healthier women were  
368 selected for estrogen therapy. In general, treated women were of higher socioeconomic  
369 and educational status, more slender, more physically active, more likely to have  
370 undergone surgical menopause, and less likely to have diabetes than the untreated  
371 women. Although some studies attempted to control for these selection factors, it is  
372 common for properly designed randomized trials to fail to confirm benefits suggested by

373 less rigorous study designs. Ongoing and future large-scale randomized trials may help to  
374 clarify the apparent benefit.

375 (2) Current medical practice often includes the use of concomitant progestin therapy in  
376 women with intact uteri (see **PRECAUTIONS** and **WARNINGS**). While the effects of  
377 added progestins on the risk of ischemic heart disease are not known, all available  
378 progestins reverse at least some of the favorable effects of estrogens on HDL and LDL  
379 levels (see **CLINICAL STUDIES**).

380 (3) While the effects of added progestins on the risk of breast cancer are also unknown,  
381 available epidemiological evidence suggests that progestins do not reduce, and  
382 may enhance the moderately increased breast cancer incidence that has been reported  
383 with prolonged estrogen replacement therapy (see **WARNINGS**).

## 384 **2. Elevated Blood Pressure**

385 Occasional blood pressure increases during estrogen replacement therapy have been  
386 attributed to idiosyncratic reactions to estrogens. More often, blood pressure has  
387 remained the same or has dropped. One study showed that postmenopausal estrogen users  
388 have higher blood pressure than nonusers.

389 Two other studies showed slightly lower blood pressure among estrogen users compared  
390 to nonusers. The data on the risk of estrogen use in postmenopausal women and the risk  
391 of stroke have not been considered conclusive. Nonetheless, blood pressure should be  
392 monitored at regular intervals with estrogen use.

## 393 **3. Use in Hysterectomized Women**

394 Existing data do not support the use of the combination of progestin and estrogen in  
395 postmenopausal women without a uterus.  
396

## 397 **4. Physical Examination**

398 A complete medical and family history should be taken prior to the initiation of *femhrt*  
399 1/5 and annually thereafter. These examinations should include special reference to blood  
400 pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolaou smear.

401 **5. Fluid Retention**

402 Progestin/estrogen therapy may cause some degree of fluid retention. Conditions which  
403 might be exacerbated by this factor such as asthma, epilepsy, migraine, and cardiac or  
404 renal dysfunction, require careful observation.

405 **6. Uterine Bleeding and Mastodynia**

406 Certain patients may develop undesirable manifestations of estrogenic stimulation, such  
407 as abnormal uterine bleeding and mastodynia. In cases of undiagnosed abnormal uterine  
408 bleeding, adequate diagnostic measures are indicated. (see **WARNINGS**)

409 **7. Impaired Liver Function**

410 Estrogens and progestins may be poorly metabolized in patients with impaired liver  
411 function. If needed, therapy should be administered with caution.

412 **8. Pathology Specimens**

413 The pathologist should be advised of progestin/estrogen therapy when relevant specimens  
414 are submitted.

415 **9. Hypercoagulability**

416 Some studies have shown that women taking estrogen replacement therapy have  
417 hypercoagulability, primarily related to decreased antithrombin activity. This effect  
418 appears dose- and duration-dependent and is less pronounced than that associated with  
419 oral contraceptive use. Also, postmenopausal women tend to have changes in coagulation  
420 parameters at baseline compared to premenopausal women. There is some suggestion that  
421 low dose postmenopausal mestranol may increase the risk of thromboembolism, although  
422 the majority of studies (of primarily conjugated estrogens users) report no such increase.  
423 There is insufficient information on hypercoagulability in women who have had previous  
424 thromboembolic disease, therefore, *femhrt* 1/5 is contraindicated in such women.

425 **10. Familial Hyperlipoproteinemia**

426 Estrogen therapy may be associated with massive elevations of plasma triglycerides  
427 leading to pancreatitis and other complications in patients with familial defects of  
428 lipoprotein metabolism.

429 **11. Depression**

430 Patients who have a history of depression should be carefully observed and the drug  
431 discontinued if the depression recurs to a serious degree.

432 **12. Impaired glucose tolerance**

433 Diabetic patients should be carefully observed while receiving progestin/estrogen  
434 therapy. The effects of *femhrt* 1/5 on glucose tolerance have not been studied.

435 **13. Lipoprotein metabolism (see Clinical Studies)**

436 **B. Information for Patients**

437 See text of Patient Package Insert which appears after the **HOW SUPPLIED** section.

438 **C. Drug/Laboratory Test Interactions**

439 **The following drug/laboratory interactions have been observed with estrogen**  
440 **therapy, and/or *femhrt* 1/5:**

- 441 1. In a 12-week study, *femhrt* 1/5 decreased Factor VII and plasminogen activator  
442 inhibitor-1 from baseline in a dose-related manner, but remained within the laboratory  
443 reference range for postmenopausal women. Mean levels of fibrinogen and partial  
444 thromboplastin time did not change from baseline for *femhrt* 1/5.
- 445 2. Estrogen therapy may increase thyroxine-binding globulin (TBG), leading to  
446 increased circulating total thyroid hormone (T4) as measured by protein-bound iodine  
447 (PBI), T4 levels (by column or radioimmunoassay), or T3 levels by  
448 radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free  
449 T4 and free T3 concentrations are unaltered.
- 450 3. Estrogen therapy may elevate other binding proteins in serum, i.e., corticosteroid  
451 binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased  
452 circulating corticosteroids and sex steroids respectively. Free or biologically active  
453 hormone concentrations are unchanged. Other plasma proteins may be increased  
454 (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

455

- 456      *femhrt* 1/5 was associated with a SHBG increase of 22%.
- 457    4. Estrogen therapy increases plasma HDL and HDL-2 subfraction concentrations,  
458      reduces LDL cholesterol concentration and increases triglyceride levels. (For effects  
459      during *femhrt* 1/5 treatment, see **Clinical Studies**).
- 460    5. Estrogen therapy is associated with impaired glucose tolerance.
- 461    6. Estrogen therapy reduces response to metyrapone test.
- 462    7. Estrogen therapy reduces serum folate concentration.

463    **D. Drug/Drug Interactions**

464    No drug-drug interaction studies have been conducted with *femhrt* 1/5.

465    The following section contains information on drug interactions with ethinyl estradiol-  
466      containing products (specifically, oral contraceptives) that have been reported in the  
467      public literature. It is unknown whether such interactions occur with *femhrt* 1/5 or drug  
468      products containing other types of estrogens.

469    **The Effects of Other Drugs on Ethinyl Estradiol**

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

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

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

480    **The Effect of Ethinyl Estradiol on Other Drugs**

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

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

491 **E. Carcinogenesis, Mutagenesis, Impairment of Fertility**

492 Long-term continuous administration of natural and synthetic estrogens in certain animal  
493 species increase the frequency of carcinomas of the breast, uterus, cervix, vagina, testis,  
494 and liver (see **CONTRAINDICATIONS AND WARNINGS**).

495 **F. Pregnancy Category X**

496 Estrogens/progestins should not be used during pregnancy (see **Contraindications and**  
497 **Warnings**).

498 **G. Nursing Mothers**

499 As a general principle, the administration of any drug to nursing mothers should be done  
500 only when clearly necessary since many drugs are excreted in human milk. Estrogen  
501 administration to nursing mothers has been shown to decrease the quantity and quality of  
502 the milk. Detectable amounts of drug have been identified in the milk of mothers  
503 receiving progestational drugs. The effect of this on the nursing infant has not been  
504 determined.

505  
506 **ADVERSE REACTIONS**

507  
508 Adverse events reported in controlled clinical studies of *femhrt* 1/5 are shown in Table 4  
509 below.

510 **Table 4. All Treatment-Emergent Adverse Events Reported at a Frequency of > 5%**  
511 **of Patients with femhrt 1/5**

512

513

| BODY SYSTEM/<br>Adverse Event  | % of Patients      |                       |
|--------------------------------|--------------------|-----------------------|
|                                | Placebo<br>N = 247 | femhrt 1/5<br>N = 258 |
| <b>BODY AS A WHOLE</b>         | <b>40.1</b>        | <b>39.5</b>           |
| Headache                       | 14.6               | 18.2                  |
| Back Pain                      | 5.3                | 4.7                   |
| Pain                           | 4.5                | 3.9                   |
| Viral Infection                | 7.9                | 7.0                   |
| Edema-Generalized              | 4.9                | 4.7                   |
| <b>DIGESTIVE SYSTEM</b>        | <b>24.4</b>        | <b>33.0</b>           |
| Nausea and/or Vomiting         | 5.3                | 7.4                   |
| Abdominal Pain                 | 4.5                | 8.1                   |
| Constipation                   | 4.0                | 3.1                   |
| <b>MUSCULOSKELETAL SYSTEM</b>  | <b>21.7</b>        | <b>20.4</b>           |
| Arthralgia                     | 6.9                | 5.8                   |
| Myalgia                        | 8.5                | 7.8                   |
| <b>PSYCHOBIOLOGIC FUNCTION</b> | <b>8.3</b>         | <b>14.1</b>           |
| Nervousness                    | 1.6                | 5.4                   |
| Depression                     | 3.6                | 5.8                   |
| <b>RESPIRATORY SYSTEM</b>      | <b>37.2</b>        | <b>35.6</b>           |
| Rhinitis                       | 15.4               | 15.1                  |
| Sinusitis                      | 9.7                | 8.1                   |
| Upper Respiratory Infection    | 4.5                | 3.9                   |
| <b>UROGENITAL SYSTEM</b>       | <b>25.0</b>        | <b>40.8</b>           |
| Breast Pain                    | 5.3                | 8.1                   |
| Urinary Tract Infection        | 3.2                | 6.2                   |
| Vaginitis                      | 4.9                | 5.4                   |

514

515

516 The following adverse events have been reported with estrogen and/or progestin therapy:

517

518 *Genitourinary system:* changes in vaginal bleeding pattern and abnormal withdrawal  
519 bleeding or flow, breakthrough bleeding, spotting, increase in size of uterine  
520 leiomyomata, vaginal candidiasis, changes in amount of cervical secretion, pre-  
521 menstrual-like syndrome, cystitis-like syndrome.

522

523 *Breasts:* tenderness, enlargement, fibrocystic disease of the breast.

524

525 *Gastrointestinal:* cholestatic jaundice, pancreatitis, flatulence, bloating, abdominal  
526 cramps.

527

528 *Skin:* chloasma or melasma that may persist when drug is discontinued, erythema  
529 multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism,  
530 itching, skin rash and pruritus.

531

532 *CNS:* headache, migraine, dizziness, chorea, insomnia.

533

534 *Cardiovascular:* changes in blood pressure, cerebrovascular accidents, deep venous  
535 thrombosis, and pulmonary embolism.

536

537 *Eyes:* intolerance to contact lenses, sudden partial or complete loss of vision, proptosis,  
538 diplopia, otosclerosis.

539

540 *Miscellaneous:* increase or decrease in weight, reduced carbohydrate tolerance,  
541 aggravation of porphyria, changes in libido, fatigue, allergic or anaphylactoid reactions,  
542 leiomyoma, fibromyoma of the uterus, endometriosis.

543 **OVERDOSAGE**

544

545 **ACUTE OVERDOSAGE**

546 Serious ill effects have not been reported following acute ingestion of large doses of  
547 progestin/estrogen-containing oral contraceptives by young children. Overdosage of  
548 estrogen may cause nausea and vomiting, and withdrawal bleeding may occur.

549 **DOSAGE AND ADMINISTRATION**

550 *femhrt* 1/5 therapy consists of a single tablet taken once daily.

551 **1. For the Treatment of Vasomotor Symptoms**

552 *femhrt* 1/5 should be given once daily for the treatment of moderate to severe vasomotor  
553 symptoms associated with the menopause. Patients should be reevaluated at 3 to 6 month  
554 intervals to determine if treatment is still necessary.

555 **2. Prevention of Osteoporosis**

556 *femhrt* 1/5 should be given once daily to prevent postmenopausal osteoporosis (see  
557 **Clinical Studies: Effect on Bone Mineral Density**) Response to therapy can be  
558 assessed by measurement of bone mineral density.

559 Treated patients with an intact uterus should be monitored closely for signs of  
560 endometrial cancer, and appropriate diagnostic measures should be taken to rule out

*femhrt*<sup>TM</sup> NA-EE  
Tablets

25 of 25  
Update as of October 15, 1999

561 malignancy in the event of persistent or recurring vaginal bleeding. Patients should be  
562 evaluated at least annually for breast abnormalities and more often if there are any  
563 symptoms.

564

565 **HOW SUPPLIED**

566 *femhrt* 1/5 tablets are white and available in the following strength and package sizes:

567 N 0071-0144-23 - Bottle of 90 D-shaped tablets with 1 mg norethindrone acetate and  
568 5 mcg ethinyl estradiol

569 N 0071-0144-45 - Blister card of 28 D-shaped tablets with 1 mg norethindrone acetate  
570 and 5 mcg ethinyl estradiol

571 Rx Only

572 **Keep this drug and all drugs out of the reach of children.**

573 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)**

574 **[see USP Controlled Room Temperature]**

575

576 Manufactured by:

577 Duramed Pharmaceuticals, Inc.

578 Cincinnati, OH 45213

579 Distributed by:

580 PARKE-DAVIS

581 Division of Warner-Lambert Co.

582 Morris Plains, NJ 07950 USA

**APPEARS THIS WAY  
ON ORIGINAL**

## INFORMATION FOR THE PATIENT

### What is *femhrt* 1/5?

Your healthcare provider has prescribed *femhrt* 1/5, a combination of two hormones, a progestin (1 mg norethindrone acetate) and an estrogen (5 mcg ethinyl estradiol) intended for use once a day. This insert describes the major benefits and risks of your treatment, as well as how and when treatment may be taken. If you have any questions, please contact your physician, nurse or pharmacist.

### *femhrt* 1/5 is approved for use in the following ways:

- **To reduce moderate to severe menopausal symptoms.** Estrogens are hormones produced by the ovaries of menstruating women. When a woman is between the ages of 45 and 55, the ovaries normally stop making estrogens. This drop in body estrogen levels causes the "change of life" or menopause, the end of monthly menstrual periods.

When estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden intense episodes of heat and sweating ("hot flashes" or "hot flushes"). In some women the symptoms are mild; in others they can be severe. These symptoms may last only a few months or longer. Taking *femhrt* 1/5 can help reduce these symptoms. If you are not taking hormones for other reasons, such as the prevention of osteoporosis, you should take *femhrt* 1/5 only as long as you need it for relief from your menopausal symptoms.

- **To prevent thinning bones (osteoporosis).** Osteoporosis is a thinning of the bones that makes them weaker and allows them to break more easily. The bones of the spine, wrists, and hips may be affected by osteoporosis. *femhrt* 1/5 may be used as part of a program including weight-bearing exercise, such as walking or running, and calcium supplements.

Women likely to develop osteoporosis often have the following characteristics: white or Asian race, slim, cigarette smokers, and a family history of osteoporosis in a mother, sister or aunt. Women who have menopause at an earlier age, either naturally or because their ovaries were removed during an operation, are more likely to develop osteoporosis than women whose menopause happens later in life.

### Who should not take *femhrt* 1/5?

*femhrt* 1/5 should not be taken in the following situations:

- **During pregnancy.** If you think you may be pregnant, do not take *femhrt* 1/5. Taking estrogens while you are pregnant may cause your unborn child to have birth defects. Do not take *femhrt* 1/5 to prevent miscarriage.
- **If you have unusual vaginal bleeding that has not been checked by your healthcare provider.** Unusual vaginal bleeding can be a warning sign of a serious condition, including cancer of the uterus, especially if bleeding happens after

menopause. Your doctor must find out the cause of the bleeding to recommend the right treatment.

- **If you have had certain cancers.** Estrogens increase the risk of certain types of cancers, including cancer of the breast and uterus. If you have had cancer, talk with your doctor about whether you should take *femhrt 1/5*.
- **If you have any circulation problems.** Generally, estrogens should not be taken if you have ever had a blood-clotting condition or other circulatory problem. In special situations, some doctors may decide that estrogen therapy is so necessary that the risks of taking *femhrt 1/5* are acceptable. (see "What are the possible risks and side effects of *femhrt 1/5*?")
- **After childbirth or when breast-feeding a baby.** *femhrt 1/5* should not be taken to try to stop the breasts from filling with milk after a baby is born. Taking *femhrt 1/5* may increase your risk of developing blood clots (see "What are the possible risks and side effects of *femhrt 1/5*?")
- **If you have had a hysterectomy (uterus removed).** *femhrt 1/5* contains a progestin to decrease the risk of developing endometrial hyperplasia (an overgrowth of the lining of the uterus that may lead to cancer). If you do not have a uterus, you do not need a progestin, and you should not take *femhrt 1/5*.

#### **How should I take *femhrt 1/5*?**

Take your *femhrt 1/5* pill once a day at about the same time each day. If you miss a dose, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and take only your next regularly scheduled dose. Do not take two doses at the same time.

The length of treatment with estrogens varies from woman to woman. You and your healthcare provider should reevaluate every 3 to 6 months whether or not you still need *femhrt 1/5* to control your hot flashes.

#### **What are the possible risks and side effects of *femhrt 1/5*?**

- **Cancer of the uterus.** *femhrt 1/5* has estrogen and progestin in it. If you take any drug that contains estrogen, including *femhrt*, you should see your doctor for regular check-ups and report any unusual vaginal bleeding right away. Vaginal bleeding after menopause may be a warning sign of a serious condition, including cancer of the uterus. Your doctor should identify the cause of any unusual vaginal bleeding. The risk of cancer of the uterus increases when estrogens are used without a progestin. The risk also increases the longer estrogens are taken and the larger the doses. You are more likely to get cancer of the uterus if you are overweight, diabetic, or have high blood pressure. *Femhrt 1/5*, which contains a progestin, reduces the estrogen-related risk of getting a condition of the uterine lining called endometrial hyperplasia. This condition may lead to cancer of the uterus (see "Other information").
- **Cancer of the breast.** Most studies have not shown a higher risk of breast cancer in women who have used estrogens. However, some studies report that breast cancer developed more often (up to twice the usual rate) in women who used estrogens for longer time periods, especially more than 10 years, or who used high doses for a

shorter time period. The effects of added progestin on the risk of breast cancer are unknown. You should have regular breast examinations by a health professional and examine your own breasts monthly. Ask your health care provider to show you how to do a breast exam yourself. If you are over 50 years of age, you should have a mammogram every year.

- **Gallbladder disease.** Women who use estrogens after menopause are more likely to develop gallbladder disease that leads to surgery than women who do not use estrogens.
- **Abnormal blood clotting.** Taking estrogens may cause changes in your blood clotting system that allow the blood to clot more easily. If blood clots form in your bloodstream, they can cut off the blood supply to vital organs, causing serious problems. These problems may include a stroke (by cutting off blood to the brain), a heart attack (by cutting off blood to the heart), or a pulmonary embolus (by cutting off blood supply to the lungs). Any of these conditions may cause death or serious long-term disability.
- **Vaginal bleeding.** With *femhrt 1/5*, menstrual-like vaginal bleeding may occur. If bleeding occurs, it is frequently light spotting or bleeding, but it may be moderate or heavy. If you experience vaginal bleeding while taking *femhrt 1/5*, discuss your bleeding pattern with your healthcare provider.

**In addition to the risks and side effects just listed, patients taking estrogen or progestin have reported the following side effects:**

- nausea and vomiting
- breast tenderness or enlargement
- headache
- retention of extra fluid (edema), which may make some conditions worse, such as asthma, epilepsy, migraine, heart disease, or kidney disease
- runny nose
- abdominal pain
- enlargement of non-cancerous tumors (fibroids) of the uterus
- spotty darkening of the skin, particularly on the face; reddening of the skin; skin rashes

**How can I reduce the risks associated with taking *femhrt 1/5*?**

If you take *femhrt 1/5*, you can reduce your risks by carefully monitoring your treatment.

**See your healthcare provider regularly.** While you take *femhrt 1/5*, see your doctor at least once a year for a checkup. If you develop vaginal bleeding while taking *femhrt 1/5*, you might need further evaluation. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram (breast x-ray), you may need more frequent breast examinations.

**Reassess your need for treatment.** Every 3-6 months, you and your doctor should discuss whether or not you still need *femhrt 1/5* for control of your hot flashes.

**Be alert for signs of trouble.** If any of the following warning signs (or any other unusual symptoms) happen while you are taking *femhrt 1/5*, call your doctor right away:

- pains in the calves or chest, sudden shortness of breath or coughing blood (possible clots in the legs, heart, or lungs)
- severe headache or vomiting, dizziness, faintness, or changes in vision or speech, weakness or numbness of an arm or leg (possible clots in the brain or eye)
- breast lumps (possible breast cancer)
- yellowing of the skin or whites of the eyes (possible liver problem)
- pain, swelling, or tenderness in the abdomen (possible gallbladder problem)

**Other Information**

- Discuss carefully with your doctor or health care provider all the possible risks and benefits of long-term estrogen and progestin treatment as they affect you personally.
- If you take calcium supplements as part of your treatment to help prevent osteoporosis, ask your doctor about the amounts recommended. A daily intake of 1500 mg of calcium is often recommended for postmenopausal women. Vitamin D (400 IU daily) may help your body use more of the calcium.
- Taking estrogens with progestins may have unhealthy effects on blood sugar, which might make a diabetic condition worse.
- Your doctor has prescribed this drug for you and you alone. Do not give your *femhrt 1/5* to anyone else. Do not take *femhrt 1/5* for conditions for which it was not prescribed.
- Keep all drugs out of the reach of children. In case of overdose, call you doctor, hospital or poison control center right away.

This leaflet provides the most important information about *femhrt 1/5*. If you want more information, ask your doctor or pharmacist for the professional labeling. The professional labeling is published in a book called "The Physicians' Desk Reference" or PDR, available in bookstores and public libraries.

APPEARS THIS WAY  
ON ORIGINAL

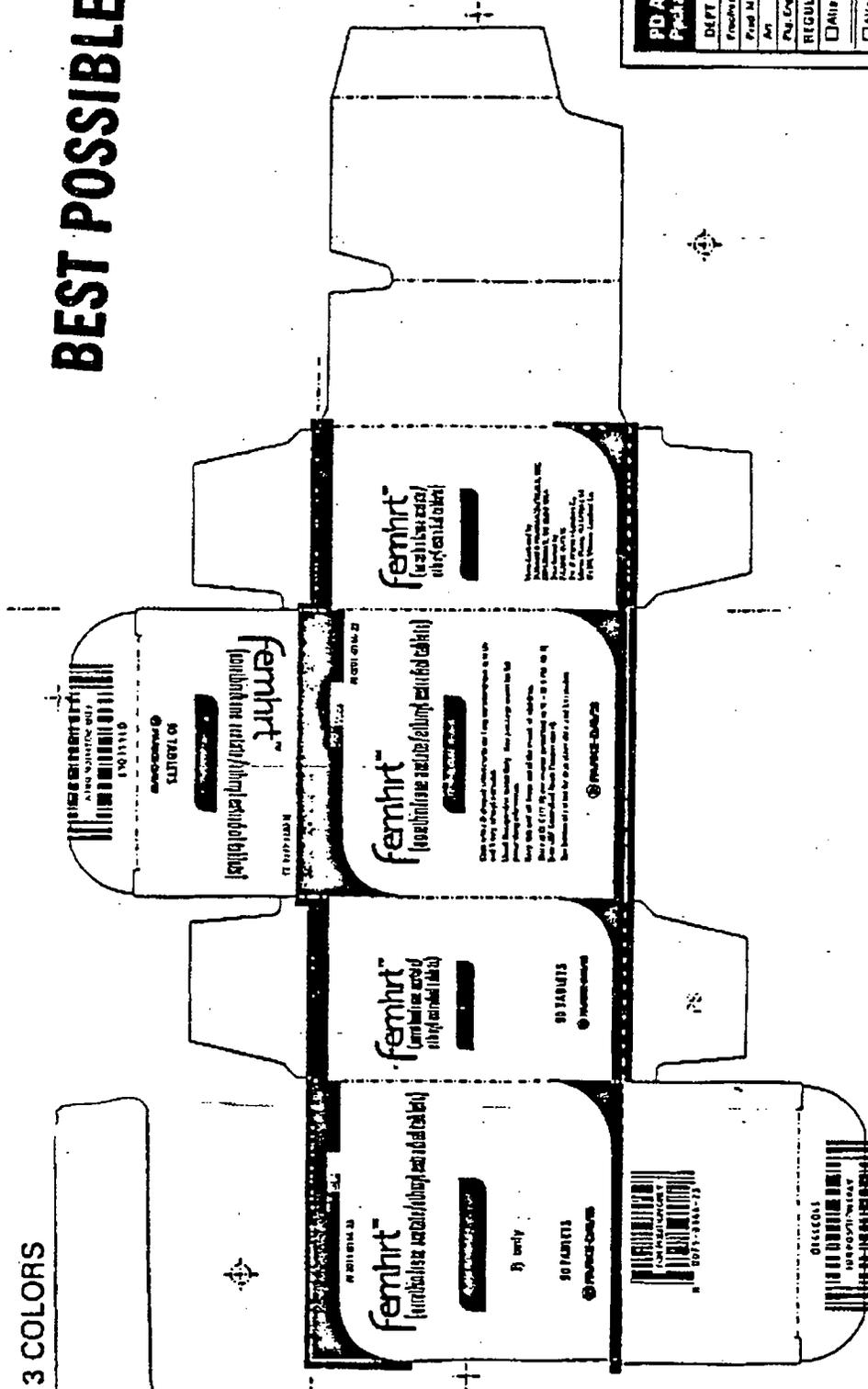
OCT 13 1999



BEST POSSIBLE COPY

3 COLORS

BEST POSSIBLE COPY



| PD Advertising Operations |                            | Package Graphic Design |      |
|---------------------------|----------------------------|------------------------|------|
| DEPT                      | SIGNATURE                  | DATE                   | DATE |
| Production                |                            |                        |      |
| Print Mgr                 |                            |                        |      |
| Art                       |                            |                        |      |
| Pre-Press                 |                            |                        |      |
| REGULATORY AFFAIRS        |                            | DATE                   | DATE |
| <input type="checkbox"/>  | Attention                  |                        |      |
| <input type="checkbox"/>  | Alteration                 |                        |      |
| <input type="checkbox"/>  | Direct Approval Req'd      |                        |      |
| <input type="checkbox"/>  | Test Approval              |                        |      |
| <input type="checkbox"/>  | Final Approval for Release |                        |      |

0143011 - Femhrt Imprint  
 PD-Brk-Box 15 - Page 0  
 Form 11/10/17 10:33 AM

W LAMBERT 2+11/16 X 1+23/32 X 2+15

FACE #16199

Stamp Capon

# BEST POSSIBLE COPY

