

1

ITEM 2.3.1.1.

2

3

4

5

6

7

8

9

femhrt 1/5

10

***femhrt* US Draft Labeling Physician Package Insert**

*femhrt*TM NA-EE
Tablets

2 of 25
Update as of October 15, 1999

11	DESCRIPTION	3
12	CLINICAL PHARMACOLOGY	3
13	Mechanism of Action	Error! Bookmark not defined.
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	Error! Bookmark not defined.
37	ACUTE OVERDOSAGE	24
38	DOSAGE AND ADMINISTRATION	24
39	HOW SUPPLIED	25

*femhrt*TM NA-EE
Tablets

3 of 25
Update as of October 15, 1999

40

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

42

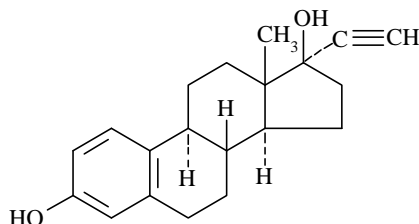
43 **DESCRIPTION**

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- α)-17-
48 (acetyloxy)-19-norpregna-4-en-20-yn-3-one] and 5 **mcg** ethinyl estradiol [(17- α)-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:

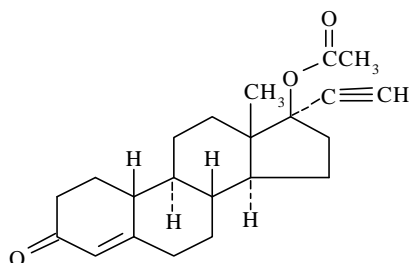


52

53 Ethinyl Estradiol

54 Molecular Weight: 296.41

55 Molecular Formula: C₂₀H₂₄O₂



56

57 Norethindrone Acetate

58 Molecular Weight: 340.47

59 Molecular Formula: C₂₂H₂₈O₃

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

*femhrt*TM NA-EE
Tablets

4 of 25

Update as of October 15, 1999

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

*femhrt*TM NA-EE
Tablets

5 of 25

Update as of October 15, 1999

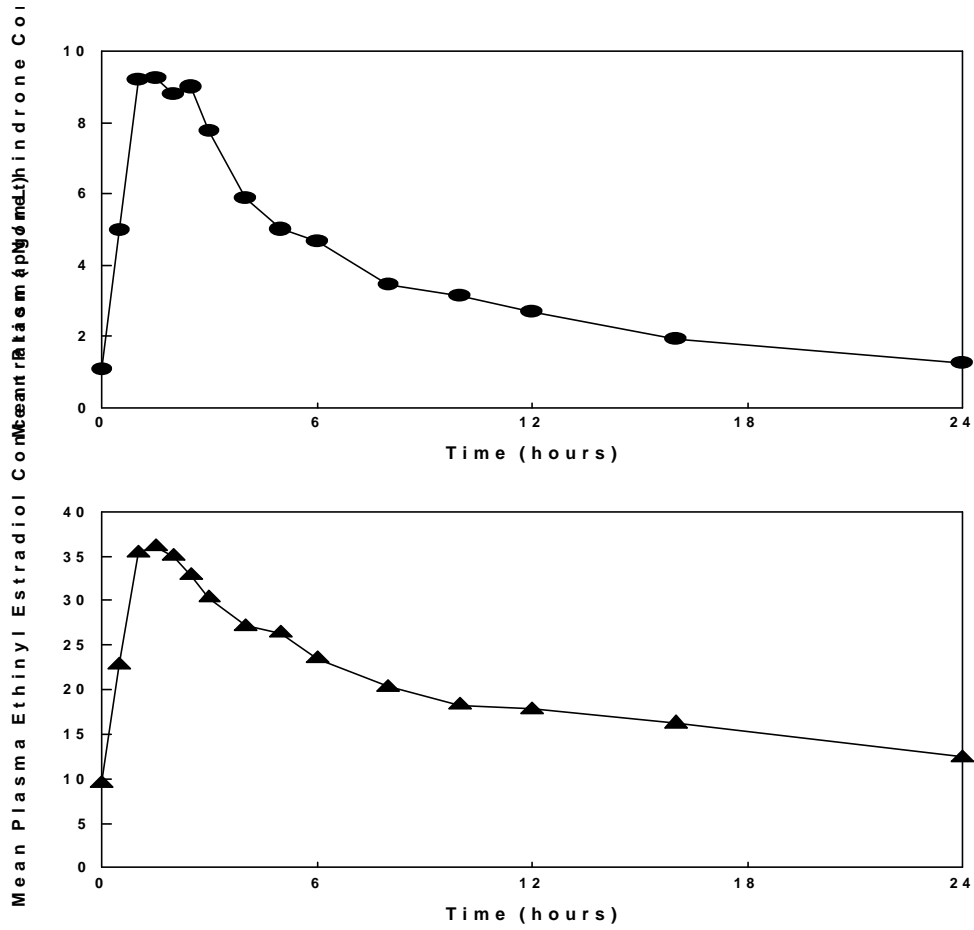
97 subject to first-pass metabolism after oral dosing, resulting in an absolute bioavailability
98 of approximately 64% for norethindrone and 55% for ethinyl estradiol. Bioavailability of
99 *femhrt* 1/5 tablets is similar to that from solution for norethindrone and slightly less for
100 ethinyl estradiol. 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.

*femhrt*TM NA-EE
Tablets

6 of 25
Update as of October 15, 1999

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

*femhrt*TM NA-EE
Tablets

7 of 25
Update as of October 15, 1999

120

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

	C _{max}	t _{max}	AUC(0-24)	CL/F	t _{1/2}
NORETHINDRONE	ng/mL	hr	ng·hr/mL	mL/min	hr
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)
ETHINYL ESTRADIOL	pg/mL	hr	pg·hr/mL	mL/min	hr
Day 1	33.5 (13.7)	2.2 (1.0)	339 (113)	ND ^b	ND ^b
Day 87	38.3 (11.9)	1.8 (0.7)	471 (132)	383 (119)	23.9 (7.1)

^a C_{max} = Maximum plasma concentration; t_{max} = time of C_{max}; AUC(0-24) = Area under the plasma concentration-time curve over the dosing interval; and CL/F = Apparent oral clearance; t_{1/2} = Elimination half-life; ^bND=Not determined

121

122 Based on a population pharmacokinetic analysis, average steady-state concentrations
123 (C_{ss}) of norethindrone and ethinyl estradiol for *femhrt* 1/5 (1mg 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

femhrt[™] NA-EE
Tablets

8 of 25

Update as of October 15, 1999

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**).

*femhrt*TM NA-EE
Tablets

9 of 25
Update as of October 15, 1999

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**

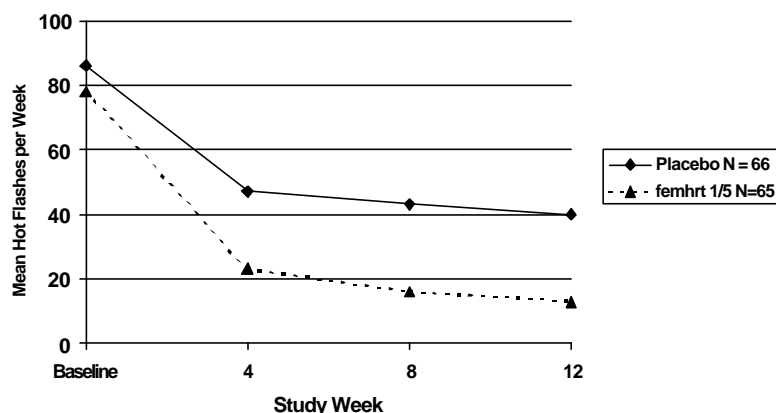
179
180 A 12-week placebo-controlled, multicenter, randomized clinical trial was conducted to
181 determine the safety and efficacy of *femhrt* 1/5 for the treatment of vasomotor symptoms.
182 The study assessed the efficacy of *femhrt* 1/5 in 266 symptomatic women who had at
183 least 56 moderate to 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.

*femhrt*TM NA-EE
Tablets

10 of 25
Update as of October 15, 1999

**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

*femhrt*TM NA-EE
Tablets

11 of 25
Update as of October 15, 1999

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

Number of Patients Biopsied at Baseline	Placebo N= 134	<i>femhrt</i> 1/5 N= 143	5 mcg ethinyl estradiol N=139
MONTH 12			
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 ^a	0	0	1
MONTH 24			
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 ^a	1	0	2

205
206
207
208
209
210
211
212
213

^aAll patients with endometrial hyperplasia were carried forward for all time points

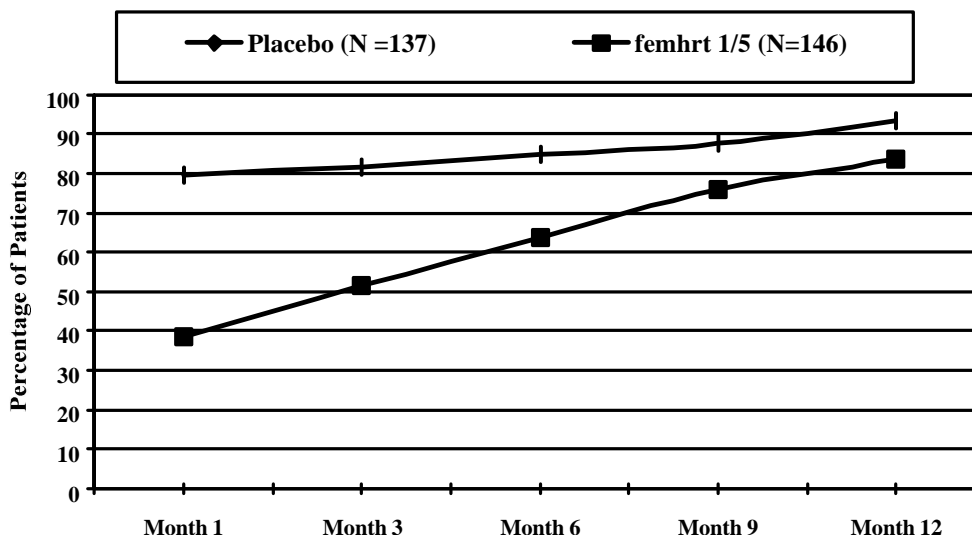
Irregular Bleeding/Spotting

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.

*femhrt*TM NA-EE
Tablets

12 of 25
Update as of October 15, 1999

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

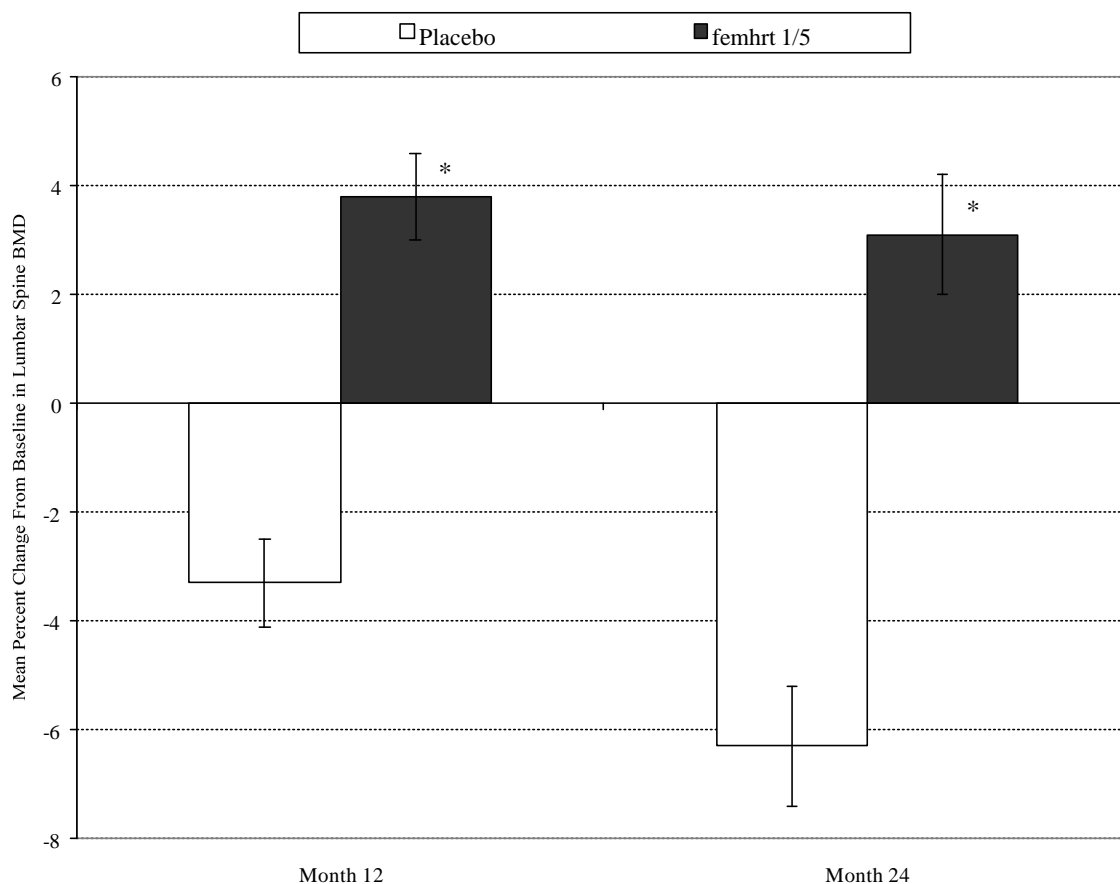
245

246

*femhrt*TM NA-EE
Tablets

13 of 25
Update as of October 15, 1999

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.

*femhrt*TM NA-EE
Tablets

14 of 25
Update as of October 15, 1999

262

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

Lipid Parameter	Placebo	<i>femhrt</i> 1/5 (mg 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

*femhrt*TM NA-EE
Tablets

15 of 25
Update as of October 15, 1999

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

*femhrt*TM NA-EE
Tablets

16 of 25
Update as of October 15, 1999

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

*femhrt*TM NA-EE
Tablets

17 of 25
Update as of October 15, 1999

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

*femhrt*TM NA-EE
Tablets

18 of 25
Update as of October 15, 1999

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.

*femhrt*TM NA-EE
Tablets

19 of 25
Update as of October 15, 1999

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.

*femhrt*TM NA-EE
Tablets

20 of 25
Update as of October 15, 1999

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

*femhrt*TM NA-EE
Tablets

21 of 25
Update as of October 15, 1999

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**

*femhrt*TM NA-EE
Tablets

22 of 25
Update as of October 15, 1999

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 clofibrac 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.

*femhrt*TM NA-EE
 Tablets

23 of 25
 Update as of October 15, 1999

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/ Adverse Event	% of Patients	
	Placebo N = 247	<i>femhrt</i> 1/5 N = 258
BODY AS A WHOLE	40.1	39.5
Headache	14.6	18.2
Back Pain	5.3	4.7
Pain	4.5	3.9
Viral Infection	7.7	7.0
Edema-Generalized	4.9	4.7
DIGESTIVE SYSTEM	24.4	33.0
Nausea and/or Vomiting	5.3	7.4
Abdominal Pain	4.5	8.1
Constipation	4.0	3.1
MUSCULOSKELETAL SYSTEM	21.7	20.4
Arthralgia	6.9	5.8
Myalgia	8.5	7.8
PSYCHOBIOLOGIC FUNCTION	8.3	14.1
Nervousness	1.6	5.4
Depression	3.6	5.8
RESPIRATORY SYSTEM	37.2	35.6
Rhinitis	15.4	15.1
Sinusitis	9.7	8.1
Upper Respiratory Infection	4.5	3.9
UROGENITAL SYSTEM	25.0	40.8
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.

*femhrt*TM NA-EE
Tablets

24 of 25
Update as of October 15, 1999

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*TM 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