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3 XXXXXXXX

4 10-29-04

5 **Femara<sup>®</sup>**  
6 **(letrozole tablets)**

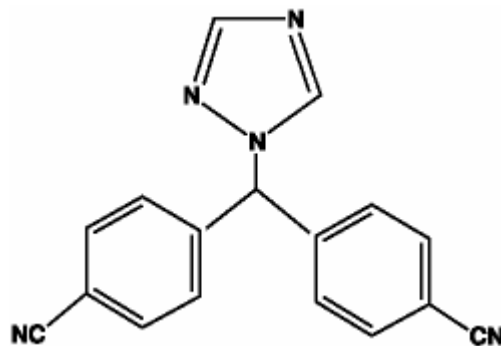
7 **2.5 mg Tablets**

8 **Rx only**

9 **Prescribing Information**

10 **DESCRIPTION**

11 Femara<sup>®</sup> (letrozole tablets) for oral administration contains 2.5 mg of letrozole, a nonsteroidal  
12 aromatase inhibitor (inhibitor of estrogen synthesis). It is chemically described as 4,4'-(1H-  
13 1,2,4-Triazol-1-ylmethylene)dibenzonitrile, and its structural formula is



14  
15 Letrozole is a white to yellowish crystalline powder, practically odorless, freely  
16 soluble in dichloromethane, slightly soluble in ethanol, and practically insoluble in water. It  
17 has a molecular weight of 285.31, empirical formula C<sub>17</sub>H<sub>11</sub>N<sub>5</sub>, and a melting range of  
18 184°C-185°C.

19 Femara<sup>®</sup> (letrozole tablets) is available as 2.5 mg tablets for oral administration.

20 *Inactive Ingredients.* Colloidal silicon dioxide, ferric oxide, hydroxypropyl  
21 methylcellulose, lactose monohydrate, magnesium stearate, maize starch, microcrystalline  
22 cellulose, polyethylene glycol, sodium starch glycolate, talc, and titanium dioxide.

23 **CLINICAL PHARMACOLOGY**

24 **Mechanism of Action**

25 The growth of some cancers of the breast is stimulated or maintained by estrogens. Treatment  
26 of breast cancer thought to be hormonally responsive (i.e., estrogen and/or progesterone  
27 receptor positive or receptor unknown) has included a variety of efforts to decrease estrogen

28 levels (ovariectomy, adrenalectomy, hypophysectomy) or inhibit estrogen effects  
29 (antiestrogens and progestational agents). These interventions lead to decreased tumor mass or  
30 delayed progression of tumor growth in some women.

31 In postmenopausal women, estrogens are mainly derived from the action of the  
32 aromatase enzyme, which converts adrenal androgens (primarily androstenedione and  
33 testosterone) to estrone and estradiol. The suppression of estrogen biosynthesis in peripheral  
34 tissues and in the cancer tissue itself can therefore be achieved by specifically inhibiting the  
35 aromatase enzyme.

36 Letrozole is a nonsteroidal competitive inhibitor of the aromatase enzyme system; it  
37 inhibits the conversion of androgens to estrogens. In adult nontumor- and tumor-bearing  
38 female animals, letrozole is as effective as ovariectomy in reducing uterine weight, elevating  
39 serum LH, and causing the regression of estrogen-dependent tumors. In contrast to  
40 ovariectomy, treatment with letrozole does not lead to an increase in serum FSH. Letrozole  
41 selectively inhibits gonadal steroidogenesis but has no significant effect on adrenal  
42 mineralocorticoid or glucocorticoid synthesis.

43 Letrozole inhibits the aromatase enzyme by competitively binding to the heme of the  
44 cytochrome P450 subunit of the enzyme, resulting in a reduction of estrogen biosynthesis in  
45 all tissues. Treatment of women with letrozole significantly lowers serum estrone, estradiol  
46 and estrone sulfate and has not been shown to significantly affect adrenal corticosteroid  
47 synthesis, aldosterone synthesis, or synthesis of thyroid hormones.

## 48 **Pharmacokinetics**

49 Letrozole is rapidly and completely absorbed from the gastrointestinal tract and absorption is  
50 not affected by food. It is metabolized slowly to an inactive metabolite whose glucuronide  
51 conjugate is excreted renally, representing the major clearance pathway. About 90% of  
52 radiolabeled letrozole is recovered in urine. Letrozole's terminal elimination half-life is about  
53 2 days and steady-state plasma concentration after daily 2.5 mg dosing is reached in 2-6  
54 weeks. Plasma concentrations at steady-state are 1.5 to 2 times higher than predicted from the  
55 concentrations measured after a single dose, indicating a slight non-linearity in the  
56 pharmacokinetics of letrozole upon daily administration of 2.5 mg. These steady-state levels  
57 are maintained over extended periods, however, and continuous accumulation of letrozole  
58 does not occur. Letrozole is weakly protein bound and has a large volume of distribution  
59 (approximately 1.9 L/kg).

## 60 **Metabolism and Excretion**

61 Metabolism to a pharmacologically-inactive carbinol metabolite (4,4'-methanol-  
62 bisbenzotrile) and renal excretion of the glucuronide conjugate of this metabolite is the  
63 major pathway of letrozole clearance. Of the radiolabel recovered in urine, at least 75% was  
64 the glucuronide of the carbinol metabolite, about 9% was two unidentified metabolites, and  
65 6% was unchanged letrozole.

66 In human microsomes with specific CYP isozyme activity, CYP3A4 metabolized  
67 letrozole to the carbinol metabolite while CYP2A6 formed both this metabolite and its ketone  
68 analog. In human liver microsomes, letrozole strongly inhibited CYP2A6 and moderately  
69 inhibited CYP2C19.

## 70 **Special Populations**

### 71 ***Pediatric, Geriatric and Race***

72 In the study populations (adults ranging in age from 35 to >80 years), no change in  
73 pharmacokinetic parameters was observed with increasing age. Differences in letrozole  
74 pharmacokinetics between adult and pediatric populations have not been studied. Differences  
75 in letrozole pharmacokinetics due to race have not been studied.

### 76 ***Renal Insufficiency***

77 In a study of volunteers with varying renal function (24-hour creatinine clearance:  
78 9-116 mL/min), no effect of renal function on the pharmacokinetics of single doses of 2.5 mg  
79 of Femara<sup>®</sup> (letrozole tablets) was found. In addition, in a study of 347 patients with advanced  
80 breast cancer, about half of whom received 2.5 mg Femara and half 0.5 mg Femara, renal  
81 impairment (calculated creatinine clearance: 20-50 mL/min) did not affect steady-state plasma  
82 letrozole concentration.

### 83 ***Hepatic Insufficiency***

84 In a study of subjects with mild to moderate non-metastatic hepatic dysfunction  
85 (e.g., cirrhosis, Child-Pugh classification A and B), the mean AUC values of the volunteers  
86 with moderate hepatic impairment were 37% higher than in normal subjects, but still within  
87 the range seen in subjects without impaired function. In a pharmacokinetics study, subjects  
88 with liver cirrhosis and severe hepatic impairment (Child-Pugh classification C, which  
89 included bilirubins about 2-11 times ULN with minimal to severe ascites) had two-fold  
90 increase in exposure (AUC) and 47% reduction in systemic clearance. Breast cancer patients  
91 with severe hepatic impairment are thus expected to be exposed to higher levels of letrozole  
92 than patients with normal liver function receiving similar doses of this drug. (See DOSAGE  
93 AND ADMINISTRATION, Hepatic Impairment.)

### 94 ***Drug/Drug Interactions***

95 A pharmacokinetic interaction study with cimetidine showed no clinically significant effect on  
96 letrozole pharmacokinetics. An interaction study with warfarin showed no clinically  
97 significant effect of letrozole on warfarin pharmacokinetics. In *in-vitro* experiments, letrozole  
98 showed no significant inhibition in the metabolism of diazepam. Similarly, no significant  
99 inhibition of letrozole metabolism by diazepam was observed.

100 Coadministration of Femara and tamoxifen 20 mg daily resulted in a reduction of  
101 letrozole plasma levels of 38% on average. Clinical experience in the second-line breast  
102 cancer pivotal trials indicates that the therapeutic effect of Femara therapy is not impaired if  
103 Femara is administered immediately after tamoxifen.

104 There is no clinical experience to date on the use of Femara in combination with other  
105 anticancer agents.

### 106 ***Pharmacodynamics***

107 In postmenopausal patients with advanced breast cancer, daily doses of 0.1 mg to 5 mg  
108 Femara suppress plasma concentrations of estradiol, estrone, and estrone sulfate by 75%-95%

109 from baseline with maximal suppression achieved within two-three days. Suppression is dose-  
110 related, with doses of 0.5 mg and higher giving many values of estrone and estrone sulfate  
111 that were below the limit of detection in the assays. Estrogen suppression was maintained  
112 throughout treatment in all patients treated at 0.5 mg or higher.

113 Letrozole is highly specific in inhibiting aromatase activity. There is no impairment of  
114 adrenal steroidogenesis. No clinically-relevant changes were found in the plasma  
115 concentrations of cortisol, aldosterone, 11-deoxycortisol, 17-hydroxy-progesterone, ACTH or  
116 in plasma renin activity among postmenopausal patients treated with a daily dose of Femara  
117 0.1 mg to 5 mg. The ACTH stimulation test performed after 6 and 12 weeks of treatment with  
118 daily doses of 0.1, 0.25, 0.5, 1, 2.5, and 5 mg did not indicate any attenuation of aldosterone  
119 or cortisol production. Glucocorticoid or mineralocorticoid supplementation is, therefore, not  
120 necessary.

121 No changes were noted in plasma concentrations of androgens (androstenedione and  
122 testosterone) among healthy postmenopausal women after 0.1, 0.5, and 2.5 mg single doses of  
123 Femara or in plasma concentrations of androstenedione among postmenopausal patients  
124 treated with daily doses of 0.1 mg to 5 mg. This indicates that the blockade of estrogen  
125 biosynthesis does not lead to accumulation of androgenic precursors. Plasma levels of LH and  
126 FSH were not affected by letrozole in patients, nor was thyroid function as evaluated by TSH  
127 levels, T3 uptake, and T4 levels.

## 128 **Clinical Studies**

### 129 **Extended Adjuvant Treatment of Early Breast Cancer in Postmenopausal Women After** 130 **Completion of 5 Years of Adjuvant Tamoxifen Therapy.**

131 A double-blind, randomized, placebo-controlled trial of Femara was performed in over 5100  
132 postmenopausal women with receptor-positive or unknown primary breast cancer who were  
133 disease-free after 5 years of adjuvant treatment with tamoxifen. Patients had to be within 3  
134 months of completing the 5 years of tamoxifen.

135 The planned duration of treatment for patients in the study was 5 years, but the trial was  
136 terminated early because of an interim analysis showing a favorable Femara effect on time  
137 without recurrence or contralateral breast cancer. At the time of unblinding, women had been  
138 followed for a median of 28 months, 30% of patients had completed 3 or more years of  
139 follow-up and less than 1% of patients had completed 5 years of follow-up.

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141 Selected baseline characteristics for the study population are shown in Table 1.

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**Table 1: Selected Study Population Demographics (Modified ITT population)**

144 <b>Baseline Status</b>	<b>Femara<sup>®</sup></b>	<b>Placebo</b>
145	<b>N=2582</b>	<b>N=2586</b>
146 Hormone receptor status (%)		
147 ER+ and/or PgR+	98	98
148 Both unknown	2	2
149 Nodal status (%)		
150 Node negative	50	50
151 Node positive	46	46

152	Nodal status unknown	4	4
153	Chemotherapy	46	46

155 Table 2 shows the study results. Disease-free survival was measured as the time from  
156 randomization to the earliest event of loco-regional or distant recurrence of the primary  
157 disease or development of contralateral breast cancer or death. Data were premature for an  
158 analysis of survival.

159 **Table 2: Extended Adjuvant Study Results**

	<b>Letrozole N = 2582</b>	<b>Placebo N = 2586</b>	<b>Hazard Ratio (95% CI)</b>	<b>P-Value</b>
<b>Disease Free Survival (DFS)</b> (First event of loco-regional recurrence, distant relapse, contralateral breast cancer or death from any cause)	122 (4.7%)	193 (7.5%)	0.62 (0.49, 0.78) <sup>1</sup>	0.00003
Local breast recurrence	9	22		
Local chest wall recurrence	2	8		
Regional recurrence	7	4		
Distant recurrence	55	92	0.61 (0.44 - 0.84)	0.003
Contralateral breast cancer	19	29		
Deaths without recurrence or contralateral breast cancer	30	38		
<b>DFS by stratification</b>				
Receptor status				
- positive	117/2527(4.6%)	190/2530(7.5%)	0.60(0.48,0.76)	
- unknown	5/55(9.1%)	3/56(5.4%)	1.78(0.43,7.5)	
nodal status				
- positive	77/1184(6.5%)	123/1187(10.4%)	0.61(0.46,0.81)	
- negative	39/1298(3.0%)	63/1301(4.8%)	0.61(0.41,0.91)	
- unknown	6/100(6.0%)	7/98(7.1%)	0.81(0.27,2.4)	
adjuvant chemotherapy				
- yes	58/1197(4.8%)	88/1199(7.3%)	0.64(0.46,0.90)	
- no	64/1385(4.6%)	105/1387(7.6%)	0.60(0.44,0.81)	

CI = confidence interval for hazard ratio. Hazard ratio of less than 1.0 indicates difference in favor of letrozole (lesser risk of recurrence); hazard ratio greater than 1.0 indicates difference in favor of placebo (higher risk of recurrence with letrozole).

<sup>1</sup> Analysis stratified by receptor status, nodal status and prior adjuvant chemotherapy (stratification factors as at randomization). P-value based on stratified logrank test.

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161 **First-Line Breast Cancer**

162 A randomized, double-blinded, multinational trial compared Femara 2.5 mg with tamoxifen  
163 20 mg in 916 postmenopausal patients with locally advanced (Stage IIIB or locoregional  
164 recurrence not amenable to treatment with surgery or radiation) or metastatic breast cancer.  
165 Time to progression (TTP) was the primary endpoint of the trial. Selected baseline  
166 characteristics for this study are shown in Table 3.

167 **Table 3: Selected Study Population Demographics**

Baseline Status	Femara® N=458	tamoxifen N=458
<b>Stage of Disease</b>		
IIIB	6%	7%
IV	93%	92%
<b>Receptor Status</b>		
ER and PgR Positive	38%	41%
ER or PgR Positive	26%	26%
Both Unknown	34%	33%
ER <sup>-</sup> or PgR <sup>-</sup> / Other Unknown	<1%	0
<b>Previous Antiestrogen Therapy</b>		
Adjuvant	19%	18%
None	81%	82%
<b>Dominant Site of Disease</b>		
Soft Tissue	25%	25%
Bone	32%	29%
Viscera	43%	46%

185 Femara was superior to tamoxifen in TTP and rate of objective tumor response (see  
186 Table 4).

187 Table 4 summarizes the results of the trial, with a total median follow-up of  
188 approximately 32 months. (All analyses are unadjusted and use 2-sided P-values.)

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**Table 4: Results**

	Femara® 2.5 mg N=453	tamoxifen 20 mg N=454	Hazard or Odds Ratio (95% CI) P-value (2-sided)
<b>Median Time to Progression</b>	9.4 months	6.0 months	0.72 (0.62, 0.83) <sup>1</sup> P<0.0001
<b>Objective Response Rate (CR + PR)</b>	145 (32%)	95 (21%)	1.77 (1.31, 2.39) <sup>2</sup> P=0.0002
<b>(CR)</b>	42 (9%)	15 (3%)	2.99 (1.63, 5.47) <sup>2</sup> P=0.0004
<b>Duration of Objective Response</b>			
Median	18 months (N=145)	16 months (N=95)	
<b>Overall Survival</b>	35 months (N=458)	32 months (N=458)	P=0.5136 <sup>3</sup>

210 <sup>1</sup> Hazard ratio

211 <sup>2</sup> Odds ratio

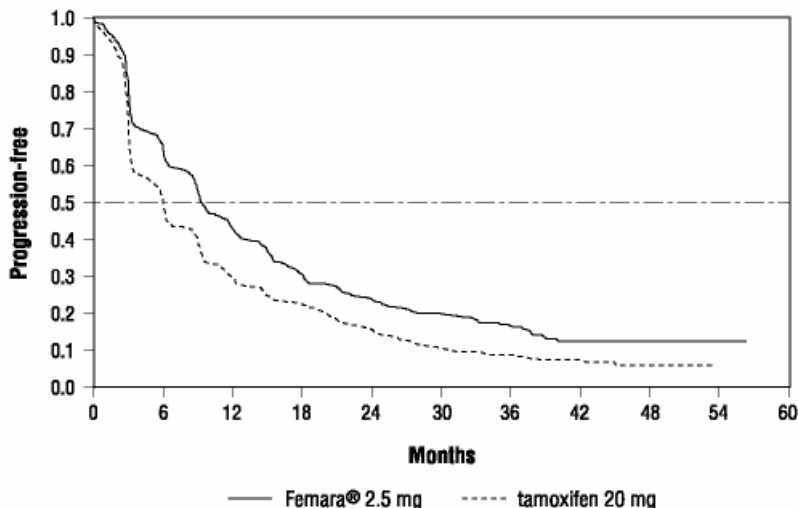
212 <sup>3</sup> Overall logrank test

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214 Figure 1 shows the Kaplan-Meier curves for TTP.

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**Figure 1**  
**Kaplan-Meier Estimates of Time to Progression**  
**(Tamoxifen Study)**



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Table 5 shows results in the subgroup of women who had received prior antiestrogen adjuvant therapy, Table 6, results by disease site and Table 7, the results by receptor status.

**Table 5: Efficacy in Patients Who Received Prior Antiestrogen Therapy**

Variable	Femara® 2.5 mg N=84	tamoxifen 20 mg N=83
<b>Median Time to Progression</b> (95% CI)	8.9 months (6.2, 12.5)	5.9 months (3.2, 6.2)
Hazard Ratio for TTP (95% CI)	0.60 (0.43, 0.84)	
<b>Objective Response Rate</b> (CR + PR)	22 (26%)	7 (8%)
Odds Ratio for Response (95% CI)	3.85 (1.50, 9.60)	

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Hazard ratio less than 1 or odds ratio greater than 1 favors letrozole; hazard ratio greater than 1 or odds ratio less than 1 favors tamoxifen.

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**Table 6: Efficacy by Disease Site**

Dominant Disease Site	Femara® 2.5 mg	tamoxifen 20 mg
<b>Soft Tissue:</b>	N=113	N=115
Median TTP	12.1 months	6.4 months
Objective Response Rate	50%	34%
<b>Bone:</b>	N=145	N=131

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248	Median TTP	9.5 months	6.3 months
249	Objective Response		
250	Rate	23%	15%
251	<b>Viscera:</b>	N=195	N=208
252	Median TTP	8.3 months	4.6 months
253	Objective Response		
254	Rate	28%	17%

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**Table 7: Efficacy by Receptor Status**

258	Variable	Femara <sup>®</sup>	tamoxifen
259		2.5 mg	20 mg
260	<b>Receptor Positive</b>	N=294	N=305
261	Median Time to		
262	Progression (95% CI)	9.4 months (8.9, 11.8)	6.0 months (5.1, 8.5)
263	Hazard Ratio for		
264	TTP (95% CI)	0.69 (0.58, 0.83)	
265	Objective Response		
266	Rate (CR+PR)	97 (33%)	66 (22%)
267	Odds Ratio for Response		
268	(95% CI)	1.78 (1.20, 2.60)	
269	<b>Receptor Unknown</b>	N=159	N=149
270	Median Time to		
271	Progression (95% CI)	9.2 months (6.1, 12.3)	6.0 months (4.1, 6.4)
272	Hazard Ratio for		
273	TTP (95% CI)	0.77 (0.60, 0.99)	
274	Objective Response		
275	Rate (CR+PR)	48 (30%)	29 (20%)
276	Odds Ratio for Response		
277	(95% CI)	1.79 (1.10, 3.00)	

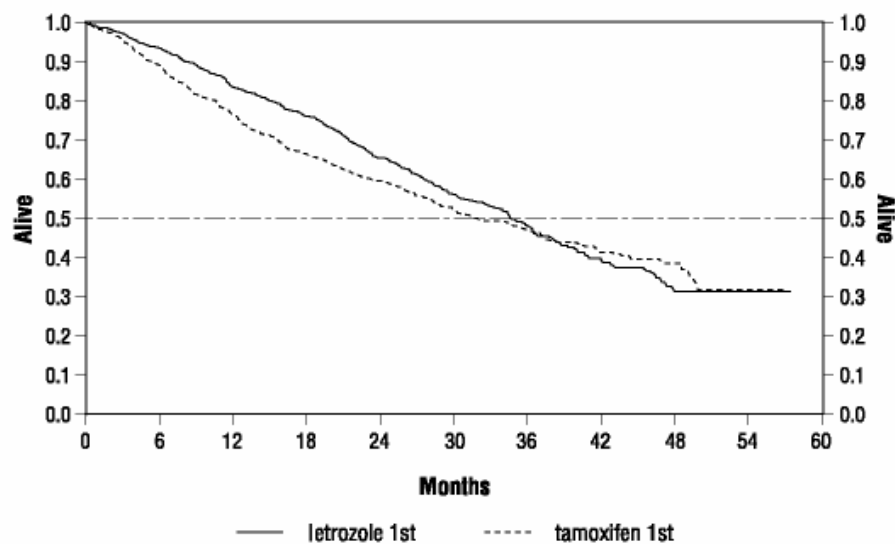
278 Hazard ratio less than 1 or odds ratio greater than 1 favors letrozole; hazard ratio greater than 1 or odds ratio less  
 279 than 1 favors tamoxifen.

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281 Figure 2 shows the Kaplan-Meier curves for survival.

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**Figure 2**  
**Survival by Randomized Treatment Arm**



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**Legend:** Randomized letrozole: n=458, events 57%, median overall survival 35 months (95% CI 32 to 38 months)  
Randomized tamoxifen: n=458, events 57%, median overall survival 32 months (95% CI 28 to 37 months)  
Overall logrank P=0.5136 (i.e., there was no significant difference between treatment arms in overall survival).

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The median overall survival was 35 months for the letrozole group and 32 months for the tamoxifen group, with a P value 0.5136.

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Study design allowed patients to crossover upon progression to the other therapy. Approximately 50% of patients crossed over to the opposite treatment arm and almost all patients who crossed over had done so by 36 months. The median time to crossover was 17 months (Femara to tamoxifen) and 13 months (tamoxifen to Femara). In patients who did not crossover to the opposite treatment arm, median survival was 35 months with Femara (n=219, 95% CI 29 to 43 months) vs. 20 months with tamoxifen (n=229, 95% CI 16 to 26 months).

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### **Second-Line Breast Cancer**

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Femara was initially studied at doses of 0.1 mg to 5.0 mg daily in six non-comparative Phase I/II trials in 181 postmenopausal estrogen/progesterone receptor positive or unknown advanced breast cancer patients previously treated with at least anti-estrogen therapy. Patients had received other hormonal therapies and also may have received cytotoxic therapy. Eight (20%) of forty patients treated with Femara 2.5 mg daily in Phase I/II trials achieved an objective tumor response (complete or partial response).

306 Two large randomized controlled multinational (predominantly European) trials were  
 307 conducted in patients with advanced breast cancer who had progressed despite antiestrogen  
 308 therapy. Patients were randomized to Femara 0.5 mg daily, Femara 2.5 mg daily, or a  
 309 comparator (megestrol acetate 160 mg daily in one study; and aminoglutethimide 250 mg  
 310 b.i.d. with corticosteroid supplementation in the other study). In each study over 60% of the  
 311 patients had received therapeutic antiestrogens, and about one-fifth of these patients had had  
 312 an objective response. The megestrol acetate controlled study was double-blind; the other  
 313 study was open label. Selected baseline characteristics for each study are shown in Table 10.

314 **Table 8: Selected Study Population Demographics**

315 <b>Parameter</b>	<b>megestrol acetate</b>	<b>aminoglutethimide</b>
316	<b>study</b>	<b>study</b>
317 <b>No. of Participants</b>	552	557
318 <b>Receptor Status</b>		
319 ER/PR Positive	57%	56%
320 ER/PR Unknown	43%	44%
321 <b>Previous Therapy</b>		
322 Adjuvant Only	33%	38%
323 Therapeutic +/- Adj.	66%	62%
324 <b>Sites of Disease</b>		
325 Soft Tissue	56%	50%
326 Bone	50%	55%
327 Viscera	40%	44%

328 Confirmed objective tumor response (complete response plus partial response) was the  
 329 primary endpoint of the trials. Responses were measured according to the Union  
 330 Internationale Contre le Cancer (UICC) criteria and verified by independent, blinded review.  
 331 All responses were confirmed by a second evaluation 4-12 weeks after the documentation of  
 332 the initial response.

333 Table 9 shows the results for the first trial, with a minimum follow-up of 15 months,  
 334 that compared Femara 0.5 mg, Femara 2.5 mg, and megestrol acetate 160 mg daily. (All  
 335 analyses are unadjusted.)

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**Table 9: Megestrol Acetate Study Results**

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	<b>Femara® 0.5 mg N=188</b>	<b>Femara® 2.5 mg N=174</b>	<b>megestrol acetate N=190</b>
<b>Objective Response (CR + PR)</b>	22 (11.7%)	41 (23.6%)	31 (16.3%)
<b>Median Duration of Response</b>	552 days	(Not reached)	561 days
<b>Median Time to Progression</b>	154 days	170 days	168 days
<b>Median Survival</b>	633 days	730 days	659 days
<b>Odds Ratio for Response</b>	Femara 2.5: Femara 0.5 = 2.33 (95% CI: 1.32, 4.17); P=0.004*		Femara 2.5: megestrol = 1.58 (95% CI: 0.94, 2.66); P=0.08*
<b>Relative Risk of Progression</b>	Femara 2.5: Femara 0.5 = 0.81 (95% CI: 0.63, 1.03); P=0.09*		Femara 2.5: megestrol = 0.77 (95% CI: 0.60, 0.98), P=0.03*

\* two-sided P-value

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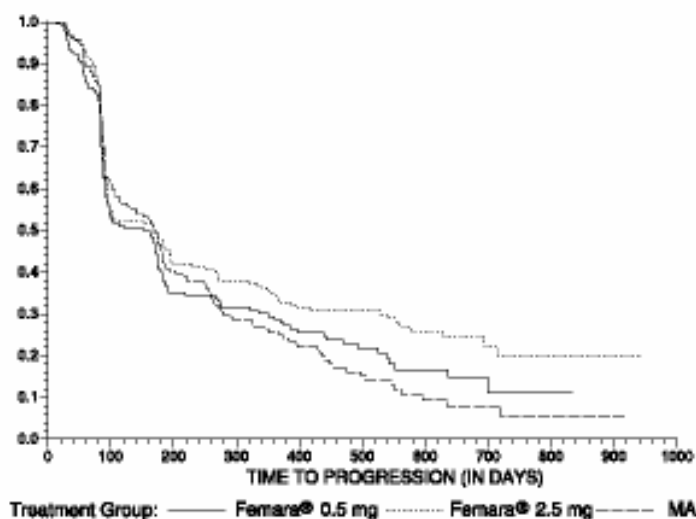
The Kaplan-Meier Curve for progression for the megestrol acetate study is shown in Figure 3.

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**Figure 3  
Kaplan-Meier Estimates of Time to Progression  
(Megestrol Acetate Study)**



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The results for the study comparing Femara to aminoglutethimide, with a minimum follow-up of nine months, are shown in Table 10. (Unadjusted analyses are used.)

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**Table 10: Aminoglutethimide Study Results**

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	<b>Femara® 0.5 mg N=193</b>	<b>Femara® 2.5 mg N=185</b>	<b>aminoglutethimide N=179</b>
<b>Objective Response (CR + PR)</b>	34 (17.6%)	34 (18.4%)	22 (12.3%)
<b>Median Duration of Response</b>	619 days	706 days	450 days
<b>Median Time To Progression</b>	103 days	123 days	112 days
<b>Median Survival</b>	636 days	792 days	592 days
<b>Odds Ratio for Response</b>	Femara 2.5: Femara 0.5=1.05 (95% CI: 0.62, 1.79); P=0.85*		Femara 2.5: aminoglutethimide=1.61 (95% CI: 0.90, 2.87); P=0.11*
<b>Relative Risk of Progression</b>	Femara 2.5: Femara 0.5=0.86 (95% CI: 0.68, 1.11); P=0.25*		Femara 2.5: aminoglutethimide=0.74 (95% CI: 0.57, 0.94), P=0.02*

\*two-sided P-value

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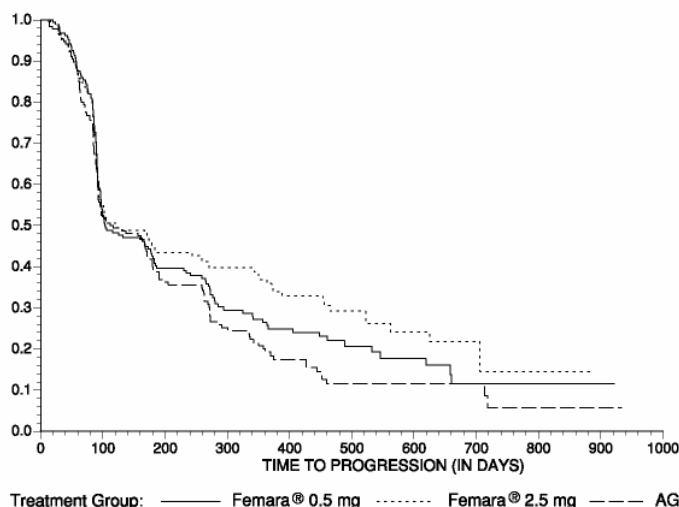
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The Kaplan-Meier Curve for progression for the aminoglutethimide study is shown in Figure 4.

**Figure 4**

**Kaplan-Meier Estimates of Time to Progression (Aminoglutethimide Study)**



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395 **INDICATIONS AND USAGE**

396 Femara<sup>®</sup> (letrozole tablets) is indicated for the extended adjuvant treatment of early breast  
397 cancer in postmenopausal women who have received 5 years of adjuvant tamoxifen therapy  
398 (see CLINICAL STUDIES). The effectiveness of Femara in extended adjuvant treatment of  
399 early breast cancer is based on an analysis of disease-free survival in patients treated for a  
400 median of 24 months (see **CLINICAL PHARMACOLOGY Clinical Studies** subsection).  
401 Further data will be required to determine long-term outcome.

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403 Femara<sup>®</sup> (letrozole tablets) is indicated for first-line treatment of postmenopausal women with  
404 hormone receptor positive or hormone receptor unknown locally advanced or metastatic  
405 breast cancer. Femara is also indicated for the treatment of advanced breast cancer in  
406 postmenopausal women with disease progression following antiestrogen therapy.

407 **CONTRAINDICATIONS**

408 Femara<sup>®</sup> (letrozole tablets) is contraindicated in patients with known hypersensitivity to  
409 Femara or any of its excipients.

410 **WARNINGS**

411 **Pregnancy**

412 Letrozole may cause fetal harm when administered to pregnant women. Studies in rats at  
413 doses equal to or greater than 0.003 mg/kg (about 1/100 the daily maximum recommended  
414 human dose on a mg/m<sup>2</sup> basis) administered during the period of organogenesis, have shown  
415 that letrozole is embryotoxic and fetotoxic, as indicated by intrauterine mortality, increased  
416 resorption, increased postimplantation loss, decreased numbers of live fetuses and fetal  
417 anomalies including absence and shortening of renal papilla, dilation of ureter, edema and  
418 incomplete ossification of frontal skull and metatarsals. Letrozole was teratogenic in rats. A  
419 0.03 mg/kg dose (about 1/10 the daily maximum recommended human dose on a mg/m<sup>2</sup>  
420 basis) caused fetal domed head and cervical/centrum vertebral fusion.

421 Letrozole is embryotoxic at doses equal to or greater than 0.002 mg/kg and fetotoxic  
422 when administered to rabbits at 0.02 mg/kg (about 1/100,000 and 1/10,000 the daily  
423 maximum recommended human dose on a mg/m<sup>2</sup> basis, respectively). Fetal anomalies  
424 included incomplete ossification of the skull, sternebrae, and fore- and hindlegs.

425 There are no studies in pregnant women. Femara<sup>®</sup> (letrozole tablets) is indicated for  
426 postmenopausal women. If there is exposure to letrozole during pregnancy, the patient should  
427 be apprised of the potential hazard to the fetus and potential risk for loss of the pregnancy.

428 **PRECAUTIONS**

429 Since fatigue and dizziness have been observed with the use of Femara<sup>®</sup> (letrozole tablets)  
430 and somnolence was uncommonly reported, caution is advised when driving or using  
431 machinery.

432 **Laboratory Tests**

433 No dose-related effect of Femara on any hematologic or clinical chemistry parameter was  
434 evident. Moderate decreases in lymphocyte counts, of uncertain clinical significance, were  
435 observed in some patients receiving Femara 2.5 mg. This depression was transient in about  
436 half of those affected. Two patients on Femara developed thrombocytopenia; relationship to  
437 the study drug was unclear. Patient withdrawal due to laboratory abnormalities, whether  
438 related to study treatment or not, was infrequent.

439 Increases in SGOT, SGPT, and gamma GT  $\geq 5$  times the upper limit of normal (ULN)  
440 and of bilirubin  $\geq 1.5$  times the ULN were most often associated with metastatic disease in the  
441 liver. About 3% of study participants receiving Femara had abnormalities in liver chemistries  
442 not associated with documented metastases; these abnormalities may have been related to  
443 study drug therapy. In the megestrol acetate comparative study about 8% of patients treated  
444 with megestrol acetate had abnormalities in liver chemistries that were not associated with  
445 documented liver metastases; in the aminoglutethimide study about 10% of  
446 aminoglutethimide-treated patients had abnormalities in liver chemistries not associated with  
447 hepatic metastases.

448 **Bone Effects**

449

450 Preliminary results (median duration of follow-up was 20 months) from the bone sub-study  
451 (Calcium 500 mg and Vitamin D 400 IU per day mandatory; bisphosphonates not allowed)  
452 demonstrated that at 2 years the mean decrease compared to baseline in hip BMD in Femara  
453 patients was 3% versus 0.4% for placebo ( $P=0.048$ ). The mean decrease from baseline BMD  
454 results for the lumbar spine at 2 years was Femara 4.6% decrease and placebo 2.2%  
455 ( $P=0.069$ ). Consideration should be given to monitoring BMD.

456

457

458 **Drug Interactions**

459 Clinical interaction studies with cimetidine and warfarin indicated that the coadministration of  
460 Femara with these drugs does not result in clinically-significant drug interactions. (See  
461 CLINICAL PHARMACOLOGY.)

462 Coadministration of Femara and tamoxifen 20 mg daily resulted in a reduction of  
463 letrozole plasma levels by 38% on average. There is no clinical experience to date on the use  
464 of Femara in combination with other anticancer agents.

465 **Hepatic Insufficiency**

466 Subjects with cirrhosis and severe hepatic dysfunction (see CLINICAL PHARMACOLOGY,  
467 Special Populations) who were dosed with 2.5 mg of Femara experienced approximately  
468 twice the exposure to letrozole as healthy volunteers with normal liver function. Therefore, a  
469 dose reduction is recommended for this patient population. The effect of hepatic impairment  
470 on Femara exposure in cancer patients with elevated bilirubin levels has not been determined.  
471 (See DOSAGE AND ADMINISTRATION.)

472 **Drug/Laboratory Test-Interactions**

473 None observed.

474 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

475 A conventional carcinogenesis study in mice at doses of 0.6 to 60 mg/kg/day (about one to  
476 100 times the daily maximum recommended human dose on a mg/m<sup>2</sup> basis) administered by  
477 oral gavage for up to 2 years revealed a dose-related increase in the incidence of benign  
478 ovarian stromal tumors. The incidence of combined hepatocellular adenoma and carcinoma  
479 showed a significant trend in females when the high dose group was excluded due to low  
480 survival. In a separate study, plasma AUC<sub>0-12hr</sub> levels in mice at 60 mg/kg/day were 55 times  
481 higher than the AUC<sub>0-24hr</sub> level in breast cancer patients at the recommended dose. The  
482 carcinogenicity study in rats at oral doses of 0.1 to 10 mg/kg/day (about 0.4 to 40 times the  
483 daily maximum recommended human dose on a mg/m<sup>2</sup> basis) for up to 2 years also produced  
484 an increase in the incidence of benign ovarian stromal tumors at 10 mg/kg/day. Ovarian  
485 hyperplasia was observed in females at doses equal to or greater than 0.1 mg/kg/day. At  
486 10 mg/kg/day, plasma AUC<sub>0-24hr</sub> levels in rats were 80 times higher than the level in breast  
487 cancer patients at the recommended dose.

488 Letrozole was not mutagenic in *in vitro* tests (Ames and E.coli bacterial tests) but was  
489 observed to be a potential clastogen in *in vitro* assays (CHO K1 and CCL 61 Chinese hamster  
490 ovary cells). Letrozole was not clastogenic *in vivo* (micronucleus test in rats).

491 Studies to investigate the effect of letrozole on fertility have not been conducted;  
492 however, repeated dosing caused sexual inactivity in females and atrophy of the reproductive  
493 tract in males and females at doses of 0.6, 0.1 and 0.03 mg/kg in mice, rats and dogs,  
494 respectively (about one, 0.4 and 0.4 the daily maximum recommended human dose on a  
495 mg/m<sup>2</sup> basis, respectively).

496 **Pregnancy**

497 **Pregnancy Category D** (see WARNINGS).

498 **Nursing Mothers**

499 It is not known if letrozole is excreted in human milk. Because many drugs are excreted in  
500 human milk, caution should be exercised when letrozole is administered to a nursing woman  
501 (see WARNINGS and PRECAUTIONS).

502 **Pediatric Use**

503 The safety and effectiveness in pediatric patients have not been established.

504 **Geriatric Use**

505 The median age of patients in all studies of first-line and second-line treatment of metastatic  
506 breast cancer was 64-65 years. About 1/3 of the patients were ≥70 years old. In the first-line  
507 study patients ≥70 years of age experienced longer time to tumor progression and higher  
508 response rates than patients <70.

509 For the extended adjuvant setting, more than 5100 postmenopausal women were enrolled in  
510 the clinical study. In total, 41% of patients were aged 65 years or older at enrollment, while  
511 12% were 75 or older. No overall differences in safety or efficacy were observed between  
512 these older patients and younger patients, and other reported clinical experience has not  
513 identified differences in responses between the elderly and younger patients, but greater  
514 sensitivity of some older individuals cannot be ruled out.  
515

## 516 **ADVERSE REACTIONS**

517 Femara<sup>®</sup> (letrozole tablets) was generally well tolerated across all studies in first-line and  
518 second-line metastatic breast cancer as well as extended adjuvant treatment in women who  
519 have received prior standard adjuvant tamoxifen treatment. Generally, the observed adverse  
520 reactions are mild or moderate in nature.

521

### 522 **Extended Adjuvant Treatment of Early Breast Cancer in Postmenopausal Women who** 523 **have Received 5 Years of Adjuvant Tamoxifen Therapy.**

524 The median duration of extended adjuvant treatment was 24 months and the median duration  
525 of follow-up for safety was 28 months for patients receiving letrozole and placebo.

526 Table 11 describes the adverse events occurring at a frequency of at least 5% in any treatment  
527 group during treatment. Most adverse events reported were grade 1 and grade 2 based on the  
528 Common Toxicity Criteria Version 2.0. In the extended adjuvant setting, the reported drug  
529 related adverse events that were significantly different from placebo were hot flashes,  
530 arthralgia/arthritis, and myalgia.

531

532

533 **Table 11 Percentage of patients with adverse events**

534

	Number (%) of patients with grade 1-4 adverse event		Number (%) of patients with grade 3-4 adverse event	
	Letrozole N=2563	Placebo N=2573	Letrozole N=2563	Placebo N=2573
<b>Any adverse event</b>	2232 (87.1)	2174 (84.5)	419 (16.3)	389 (15.1)
<b>Vascular disorders</b>	1375 (53.6)	1230 (47.8)	59 (2.3)	74 (2.9)
Flushing	1273 (49.7)	1114 (43.3)	3 (0.1)	0
<b>General disorders</b>	1154 (45.0)	1090 (42.4)	30 (1.2)	28 (1.1)
Asthenia	862 (33.6)	826 (32.1)	16 (0.6)	7 (0.3)
Edema NOS	471 (18.4)	416 (16.2)	4 (0.2)	3 (0.1)
<b>Musculoskeletal disorders</b>	978 (38.2)	836 (32.5)	71 (2.8)	50 (1.9)
Arthralgia	565 (22.0)	465 (18.1)	25 (1.0)	20 (0.8)
Arthritis NOS	173 (6.7)	124 (4.8)	10 (0.4)	5 (0.2)
Myalgia	171 (6.7)	122 (4.7)	8 (0.3)	6 (0.2)
Back pain	129 (5.0)	112 (4.4)	8 (0.3)	7 (0.3)

<b>Nervous system disorders</b>	863 (33.7)	819 (31.8)	65 (2.5)	58 (2.3)
Headache	516 (20.1)	508 (19.7)	18 (0.7)	17 (0.7)
Dizziness	363 (14.2)	342 (13.3)	9 (0.4)	6 (0.2)
<b>Skin disorders</b>	830 (32.4)	787 (30.6)	17 (0.7)	16 (0.6)
Sweating increased	619 (24.2)	577 (22.4)	1 (<0.1)	0
<b>Gastrointestinal disorders</b>	725 (28.3)	731 (28.4)	43 (1.7)	42 (1.6)
Constipation	290 (11.3)	304 (11.8)	6 (0.2)	2 (<0.1)
Nausea	221 (8.6)	212 (8.2)	3 (0.1)	10 (0.4)
Diarrhea NOS	128 (5.0)	143 (5.6)	12 (0.5)	8 (0.3)
<b>Metabolic disorders</b>	551 (21.5)	537 (20.9)	24 (0.9)	32 (1.2)
Hypercholesterolaemia	401 (15.6)	398 (15.5)	2 (<0.1)	5 (0.2)
<b>Reproductive disorders</b>	303 (11.8)	357 (13.9)	9 (0.4)	8 (0.3)
Vaginal haemorrhage	123 (4.8)	171 (6.6)	2 (<0.1)	5 (0.2)
Vulvovaginal dryness	137 (5.3)	127 (4.9)	0	0
<b>Psychiatric disorders</b>	320 (12.5)	276 (10.7)	21 (0.8)	16 (0.6)
Insomnia	149 (5.8)	120 (4.7)	2 (<0.1)	2 (<0.1)
<b>Respiratory disorders</b>	279 (10.9)	260 (10.1)	30 (1.2)	28 (1.1)
Dyspnoea	140 (5.5)	137 (5.3)	21 (0.8)	18 (0.7)
<b>Investigations</b>	184 (7.2)	147 (5.7)	13 (0.5)	13 (0.5)
<b>Infections and infestations</b>	166 (6.5)	163 (6.3)	40 (1.6)	33 (1.3)
<b>Renal disorders</b>	130 (5.1)	100 (3.9)	12 (0.5)	6 (0.2)

535

536

537

538 The duration of follow-up for both the main clinical study and the bone study were  
 539 insufficient to assess fracture risk associated with long-term use of letrozole. Based on a  
 540 median follow-up of patients for 28 months, the incidence of clinical fractures from the core  
 541 randomized study in patients who received Femara was 5.9% (152) and placebo was 5.5%  
 542 (142). The incidence of self-reported osteoporosis was higher in patients who received  
 543 Femara 6.9% (176) than in patients who received placebo 5.5% (141). Bisphosphonates were  
 544 administered to 21.1% of the patients who received Femara and 18.7% of the patients who  
 545 received placebo.

546 Preliminary results (median duration of follow-up was 20 months) from the bone sub-study  
 547 (Calcium 500 mg and Vitamin D 400 IU per day mandatory; bisphosphonates not allowed)  
 548 demonstrated that at 2 years the mean decrease compared to baseline in hip BMD in Femara  
 549 patients was 3% versus 0.4% for placebo. The mean decrease from baseline BMD results for  
 550 the lumbar spine at 2 years were Femara 4.6% decrease and placebo 2.2%.

551 The incidence of cardiovascular ischemic events from the core randomized study was  
 552 comparable between patients who received Femara 6.8% (175) and placebo 6.5% (167).

553 Preliminary results (median duration of follow-up was 30 months) from the lipid sub-study  
 554 did not show significant differences between the Femara and placebo groups. The HDL:LDL  
 555 ratio decreased after the first 6 months of therapy but the decrease was similar in both groups  
 556 and no statistically significant differences were detected.

557 . A patient-reported measure that captures treatment impact on important symptoms  
558 associated with estrogen deficiency demonstrated a difference in favour of placebo for  
559 vasomotor and sexual symptom domains."

#### 560 **First-Line Breast Cancer**

561 A total of 455 patients was treated for a median time of exposure of 11 months. The incidence  
562 of adverse experiences was similar for Femara and tamoxifen. The most frequently reported  
563 adverse experiences were bone pain, hot flushes, back pain, nausea, arthralgia and dyspnea.  
564 Discontinuations for adverse experiences other than progression of tumor occurred in 10/455  
565 (2%) of patients on Femara and in 15/455 (3%) of patients on tamoxifen.

566 Adverse events, regardless of relationship to study drug, that were reported in at least  
567 5% of the patients treated with Femara 2.5 mg or tamoxifen 20 mg in the first-line treatment  
568 study are shown in Table 12.

569

**Table 12: Percentage (%) of Patients with Adverse Events**

570	<b>Adverse</b>	<b>Femara®</b>	<b>tamoxifen</b>
571	<b>Experience</b>	<b>2.5 mg</b>	<b>20 mg</b>
572		<b>(N=455)</b>	<b>(N=455)</b>
573		<b>%</b>	<b>%</b>
574	<b>General Disorders</b>		
575	Fatigue	13	13
576	Chest pain	8	9
577	Edema peripheral	5	6
578	Pain not otherwise specified	5	7
579	Weakness	6	4
580	<b>Investigations</b>		
581	Weight decreased	7	5
582	<b>Vascular Disorders</b>		
583	Hot flushes	19	16
584	Hypertension	8	4
585	<b>Gastrointestinal Disorders</b>		
586	Nausea	17	17
587	Constipation	10	11
588	Diarrhea	8	4
589	Vomiting	7	8
590	<b>Infections/Infestations</b>		
591	Influenza	6	4
592	Urinary tract infection		
593	not otherwise specified	6	3
594	<b>Injury, Poisoning and Procedural Complications</b>		
595	Post-mastectomy lymphedema	7	7
596	<b>Metabolism and Nutrition Disorders</b>		
597	Anorexia	4	6
598	<b>Musculoskeletal and Connective Tissue Disorders</b>		
599	Bone pain	22	21
600	Back pain	18	19
601	Arthralgia	16	15
602	Pain in limb	10	8
603	<b>Nervous System Disorders</b>		
604	Headache not otherwise specified	8	7
605	<b>Psychiatric Disorders</b>		
606	Insomnia	7	4
607	<b>Reproductive System and Breast Disorders</b>		
608	Breast Pain	7	7
609	<b>Respiratory, Thoracic and Mediastinal Disorders</b>		
610	Dyspnea	18	17
611	Cough	13	13
612	Chest wall pain	6	6

613 Other less frequent ( $\leq 2\%$ ) adverse experiences considered consequential for both  
614 treatment groups, included peripheral thromboembolic events, cardiovascular events, and  
615 cerebrovascular events. Peripheral thromboembolic events included venous thrombosis,  
616 thrombophlebitis, portal vein thrombosis and pulmonary embolism. Cardiovascular events  
617 included angina, myocardial infarction, myocardial ischemia, and coronary heart disease.  
618 Cerebrovascular events included transient ischemic attacks, thrombotic or hemorrhagic  
619 strokes and development of hemiparesis.

620 **Second-Line Breast Cancer**

621 Femara was generally well tolerated in two controlled clinical trials.

622 Study discontinuations in the megestrol acetate comparison study for adverse events  
623 other than progression of tumor occurred in 5/188 (2.7%) of patients on Femara 0.5 mg, in  
624 4/174 (2.3%) of the patients on Femara 2.5 mg, and in 15/190 (7.9%) of patients on megestrol  
625 acetate. There were fewer thromboembolic events at both Femara doses than on the megestrol  
626 acetate arm (2 of 362 patients or 0.6% vs. 9 of 190 patients or 4.7%). There was also less  
627 vaginal bleeding (1 of 362 patients or 0.3% vs. 6 of 190 patients or 3.2%) on letrozole than on  
628 megestrol acetate. In the aminoglutethimide comparison study, discontinuations for reasons  
629 other than progression occurred in 6/193 (3.1%) of patients on 0.5 mg Femara, 7/185 (3.8%)  
630 of patients on 2.5 mg Femara, and 7/178 (3.9%) of patients on aminoglutethimide.

631 Comparisons of the incidence of adverse events revealed no significant differences  
632 between the high and low dose Femara groups in either study. Most of the adverse events  
633 observed in all treatment groups were mild to moderate in severity and it was generally not  
634 possible to distinguish adverse reactions due to treatment from the consequences of the  
635 patient's metastatic breast cancer, the effects of estrogen deprivation, or intercurrent illness.

636 Adverse events, regardless of relationship to study drug, that were reported in at least  
637 5% of the patients treated with Femara 0.5 mg, Femara 2.5 mg, megestrol acetate, or  
638 aminoglutethimide in the two controlled trials are shown in Table 13.

640 **Table 13: Percentage (%) of Patients with Adverse Events**

641 Adverse 642 Experience	643 Pooled 644 Femara® 645 2.5 mg (N=359) 646 %	647 Pooled 648 Femara® 649 0.5 mg (N=380) 650 %	651 megestrol 652 acetate 653 160 mg (N=189) 654 %	655 aminoglutethimide 656 500 mg (N=178) 657 %
<b>658 Body as a Whole</b>				
659 Fatigue	8	6	11	3
660 Chest pain	6	3	7	3
661 Peripheral edema <sup>1</sup>	5	5	8	3
662 Asthenia	4	5	4	5
663 Weight increase	2	2	9	3
<b>664 Cardiovascular</b>				
665 Hypertension	5	7	5	6
<b>666 Digestive System</b>				
667 Nausea	13	15	9	14
668 Vomiting	7	7	5	9
669 Constipation	6	7	9	7
670 Diarrhea	6	5	3	4
671 Pain-abdominal	6	5	9	8
672 Anorexia	5	3	5	5
673 Dyspepsia	3	4	6	5
<b>674 Infections/Infestations</b>				
675 Viral infection	6	5	6	3
<b>676 Lab Abnormality</b>				
677 Hypercholesterolemia	3	3	0	6
<b>678 Musculoskeletal System</b>				
679 Musculoskeletal <sup>2</sup>	21	22	30	14
680 Arthralgia	8	8	8	3

669	<b>Nervous System</b>				
670	Headache	9	12	9	7
671	Somnolence	3	2	2	9
672	Dizziness	3	5	7	3
673	<b>Respiratory System</b>				
674	Dyspnea	7	9	16	5
675	Coughing	6	5	7	5
676	<b>Skin and Appendages</b>				
677	Hot flushes	6	5	4	3
678	Rash <sup>3</sup>	5	4	3	12
679	Pruritus	1	2	5	3

680 <sup>1</sup> Includes peripheral edema, leg edema, dependent edema, edema

681 <sup>2</sup> Includes musculoskeletal pain, skeletal pain, back pain, arm pain, leg pain

682 <sup>3</sup> Includes rash, erythematous rash, maculopapular rash, psoriasiform rash, vesicular rash

683 Other less frequent (<5%) adverse experiences considered consequential and reported  
684 in at least 3 patients treated with Femara, included hypercalcemia, fracture, depression,  
685 anxiety, pleural effusion, alopecia, increased sweating and vertigo.

### 686 **Post-Marketing Experiences**

687 Cases of blurred vision and increased hepatic enzyme have been uncommonly (<1%) reported  
688 since market introduction.

## 689 **OVERDOSAGE**

690 Isolated cases of Femara<sup>®</sup> (letrozole tablets) overdose have been reported. In these instances,  
691 the highest single dose ingested was 62.5 mg or 25 tablets. While no serious adverse events  
692 were reported in these cases, because of the limited data available, no firm recommendations  
693 for treatment can be made. However, emesis could be induced if the patient is alert. In  
694 general, supportive care and frequent monitoring of vital signs are also appropriate. In single  
695 dose studies the highest dose used was 30 mg, which was well tolerated; in multiple dose  
696 trials, the largest dose of 10 mg was well tolerated.

697 Lethality was observed in mice and rats following single oral doses that were equal to  
698 or greater than 2000 mg/kg (about 4000 to 8000 times the daily maximum recommended  
699 human dose on a mg/m<sup>2</sup> basis); death was associated with reduced motor activity, ataxia and  
700 dyspnea. Lethality was observed in cats following single IV doses that were equal to or  
701 greater than 10 mg/kg (about 50 times the daily maximum recommended human dose on a  
702 mg/m<sup>2</sup> basis); death was preceded by depressed blood pressure and arrhythmias.

## 703 **DOSAGE AND ADMINISTRATION**

### 704 **Adult and Elderly Patients**

705 The recommended dose of Femara<sup>®</sup> (letrozole tablets) is one 2.5 mg tablet administered once  
706 a day, without regard to meals. In patients with advanced disease, treatment with Femara  
707 should continue until tumor progression is evident. In the extended adjuvant setting, the  
708 optimal treatment duration with Femara is not known. The planned duration of treatment in  
709 the study was 5 years. However, at the time of the analysis, the median treatment duration  
710 was 24 months, 25% of patients were treated for at least 3 years and less than 1% of patients

711 were treated for the planned duration of 5 years. The median duration of follow-up was 28  
712 months. Treatment should be discontinued at tumor relapse (see CLINICAL STUDIES).

713

714

715 No dose adjustment is required for elderly patients. Patients treated with Femara do not  
716 require glucocorticoid or mineralocorticoid replacement therapy.

### 717 **Renal Impairment**

718 (See CLINICAL PHARMACOLOGY.) No dosage adjustment is required for patients with  
719 renal impairment if creatinine clearance is  $\geq 10$  mL/min.

### 720 **Hepatic Impairment**

721 No dosage adjustment is recommended for patients with mild to moderate hepatic impairment,  
722 although letrozole blood concentrations were modestly increased in subjects with moderate  
723 hepatic impairment due to cirrhosis. The dose of letrozole in patients with cirrhosis and severe  
724 hepatic dysfunction should be reduced by 50% (see CLINICAL PHARMACOLOGY). The  
725 recommended dose of Femara<sup>®</sup> (letrozole tablets) for such patients is 2.5 mg administered  
726 every other day. The effect of hepatic impairment on Femara exposure in noncirrhotic cancer  
727 patients with elevated bilirubin levels has not been determined. (See CLINICAL  
728 PHARMACOLOGY.)

### 729 **HOW SUPPLIED**

730 2.5 mg tablets - dark yellow, film-coated, round, slightly biconvex, with beveled edges  
731 (imprinted with the letters FV on one side and CG on the other side).

732 Packaged in HDPE bottles with a safety screw cap.

733 Bottles of 30 tablets .....NDC 0078-0249-15

734 Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F). [See USP Controlled  
735 Room Temperature].

736

737 T200X-XX

738 REV: XXXX 200X

Printed in U.S.A.

XXXXXXXXXX

739

740  **NOVARTIS**

741

742 Novartis Pharmaceuticals Corporation

743 East Hanover, New Jersey 07936