

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

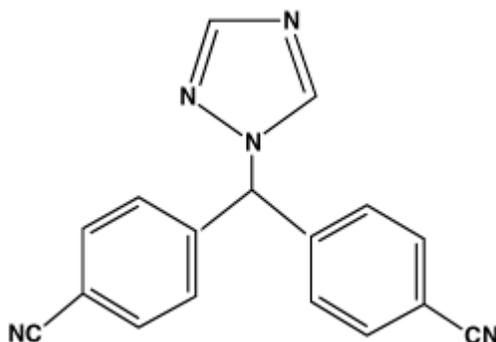
7 **2.5 mg Tablets**

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  
30 or 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  
54 2-6 weeks. Plasma concentrations at steady-state are 1.5 to 2 times higher than predicted from  
55 the 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  
96 on 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 Co-administration of Femara and tamoxifen 20 mg daily resulted in a reduction of letrozole  
101 plasma levels of 38% on average. Clinical experience in the second-line breast cancer pivotal  
102 trials indicates that the therapeutic effect of Femara therapy is not impaired if Femara is  
103 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

110 dose-related, with doses of 0.5 mg and higher giving many values of estrone and estrone  
 111 sulfate that were below the limit of detection in the assays. Estrogen suppression was  
 112 maintained 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  
 114 of 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  
 126 and FSH were not affected by letrozole in patients, nor was thyroid function as evaluated by  
 127 TSH levels, T3 uptake, and T4 levels.

## 128 **Clinical Studies**

### 129 ***First-Line Breast Cancer***

130 A randomized, double-blinded, multinational trial compared Femara 2.5 mg with tamoxifen  
 131 20 mg in 907 postmenopausal patients with locally advanced (Stage IIIB or locoregional  
 132 recurrence not amenable to treatment with surgery or radiation) or metastatic breast cancer.  
 133 Time to progression (TTP) was the primary endpoint of the trial. Selected baseline  
 134 characteristics for this study are shown in Table 1.

135 **Table 1: Selected Study Population Demographics**

136 <b>Baseline Status</b>	<b>Femara®</b> N = 453	<b>tamoxifen</b> N = 454
138 <b>Stage of Disease</b>		
139 IIIB	6%	7%
140 IV	93%	92%
141 <b>Receptor Status</b>		
142 ER and PR Positive	38%	41%
143 ER or PR Positive	26%	26%
144 Both unknown	34%	33%
145 ER <sup>-</sup> or PR <sup>-</sup> / other unknown	<1%	0
146 <b>Previous Antiestrogen Therapy</b>		
147 Adjuvant	19%	18%
148 None	81%	82%
149 <b>Dominant Site of Disease</b>		
150 Soft Tissue	25%	25%
151 Bone	32%	29%
152 Visceral	43%	46%

153 Femara was superior to tamoxifen in TTP and rate of objective tumor response  
 154 (see Table 2). No differences were seen in duration of tumor response. Results from the

155 prospectively defined secondary endpoint of time to treatment failure and clinical benefit  
156 were supportive of the results of the primary efficacy endpoint.

157 Table 2 summarizes the results of the trial, with a total median follow-up of  
158 approximately 18 months. (All analyses are unadjusted and use 2-sided p-values.)

159 **Table 2: Results**

	<b>Femara® 2.5 mg N = 453</b>	<b>tamoxifen 20 mg N = 454</b>	<b>ratio (95% CI) p-value (2-sided)</b>
163 <b>Median Time 164 to Progression</b>	9.4 months	6.0 months	0.70 (0.60, 0.82) <sup>1</sup> p=0.0001
166 <b>Objective Response 167 Rate 168 (CR + PR) 169 (CR)</b>	137 (30%) 34 (8%)	92 (20%) 13 (3%)	1.71 (1.26, 2.32) <sup>2</sup> p=0.0006 2.75 (1.43, 5.29) <sup>2</sup> p=0.002

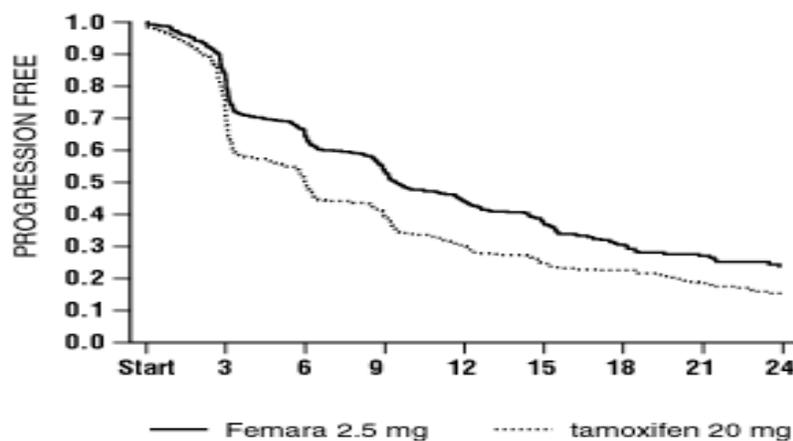
172  
173 <sup>1</sup> Hazard ratio

174 <sup>2</sup> Odds ratio

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

176 Table 3 shows results in the subgroup and women who had received prior antiestrogen  
177 adjuvant therapy and Table 4 shows results by disease site.

178 **Figure 1**  
179 **KAPLAN-MEIER ESTIMATES OF TIME TO PROGRESSION**  
180 **(TAMOXIFEN STUDY)**



181

182

183 **Table 3:**  
184 **Efficacy in Patients Who Received Prior Antiestrogen Adjuvant Therapy**

	<b>Femara® 2.5 mg N = 84</b>	<b>tamoxifen 20 mg N = 83</b>	<b>p-value (2-sided)</b>
185			
186			
187			

188	<b>Median Time To Progression</b>	8.8 months	5.9 months	0.04 <sup>1</sup>
189	<b>Objective Response Rate</b>			
190	<b>(CR + PR)</b>	29%	8%	0.002 <sup>2</sup>
191	<hr/>			
192	<sup>1</sup> Hazard ratio			
193	<sup>2</sup> Odds ratio			

Table 4: Efficacy by Disease Site

195		<b>Femara®</b>	<b>tamoxifen</b>	
196		<b>2.5 mg</b>	<b>20 mg</b>	<b>p-value</b>
197		<b>N = 453</b>	<b>N = 454</b>	<b>(2-sided)</b>
198	<b>Dominant Disease Site</b>			
199	<b>Soft Tissue:</b>	N = 113	N = 116	
200	Median TTP	12.9 months	6.4 months	0.05 <sup>1</sup>
201	Objective Response			
202	Rate	48%	35%	0.04 <sup>2</sup>
203	<b>Bone:</b>	N = 146	N = 130	
204	Median TTP	9.7 months	6.2 months	0.01 <sup>1</sup>
205	Objective Response			
206	Rate	22%	14%	0.08 <sup>2</sup>
207	<b>Visceral:</b>	N = 194	N = 208	
208	Median TTP	8.2 months	4.7 months	0.001 <sup>1</sup>
209	Objective Response			
210	Rate	26%	16%	0.02 <sup>2</sup>
211	<hr/>			
212	<sup>1</sup> Hazard ratio			
213	<sup>2</sup> Odds ratio			

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

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

221 Two large randomized controlled multinational (predominantly European) trials were  
 222 conducted in patients with advanced breast cancer who had progressed despite antiestrogen  
 223 therapy. Patients were randomized to Femara 0.5 mg daily, Femara 2.5 mg daily, or a  
 224 comparator (megestrol acetate 160 mg daily in one study; and aminoglutethimide  
 225 250 mg b.i.d. with corticosteroid supplementation in the other study). In each study over 60%  
 226 of the patients had received therapeutic antiestrogens, and about one-fifth of these patients  
 227 had had an objective response. The megestrol acetate controlled study was double-blind; the  
 228 other study was open label. Selected baseline characteristics for each study are shown in  
 229 Table 5.

Table 5: Selected Study Population Demographics

231	<b>Parameter</b>	<b>megestrol acetate</b>	<b>aminoglutethimide</b>
232		<b>study</b>	<b>study</b>
	<hr/>		

233	<b>No. of Participants</b>	552	557
234	<b>Receptor Status</b>		
235	ER/PR Positive	57%	56%
236	ER/PR Unknown	43%	44%
237	<b>Previous Therapy</b>		
238	Adjuvant Only	33%	38%
239	Therapeutic +/- Adj.	66%	62%
240	<b>Sites of Disease</b>		
241	Soft Tissue	56%	50%
242	Bone	50%	55%
243	Visceral	40%	44%

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

249 Table 6 shows the results for the first trial, with a minimum follow-up of 15 months,  
 250 that compared Femara 0.5 mg, Femara 2.5 mg, and megestrol acetate 160 mg daily. (All  
 251 analyses are unadjusted.)

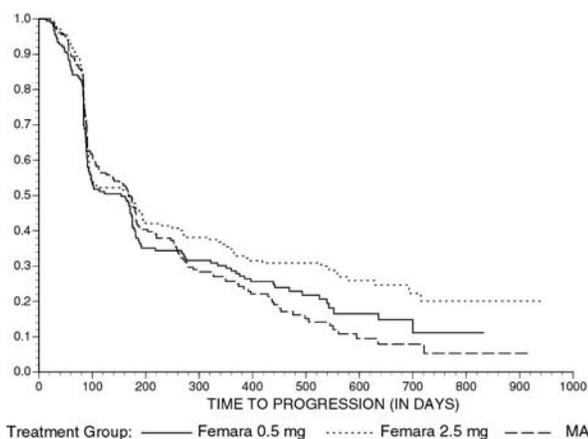
252 **Table 6: Megestrol Acetate Study Results**

253	<b>Femara<sup>®</sup></b>	<b>Femara<sup>®</sup></b>	<b>megestrol</b>
254	<b>0.5 mg</b>	<b>2.5 mg</b>	<b>acetate</b>
255	<b>N = 188</b>	<b>N = 174</b>	<b>N = 190</b>
256	<b>Objective Response</b>		
257	<b>(CR + PR)</b>	22 (11.7%)	41 (23.6%)
258	<b>Median Duration</b>		
259	<b>of Response</b>	552 days	(Not reached)
260	<b>Median Time</b>		
261	<b>to Progression</b>	154 days	170 days
262	<b>Median Survival</b>		
263	633 days		
264	<b>Odds Ratio</b>		
265	<b>for Response</b>		
266	Femara 2.5: Femara 0.5 = 2.33		Femara 2.5: megestrol = 1.58
267	(95% CI: 1.32, 4.17); p=0.004*		(95% CI: 0.94, 2.66); p=0.08*
268	<b>Relative Risk</b>		
269	<b>of Progression</b>		
270	Femara 2.5: Femara 0.5 = 0.81		Femara 2.5: megestrol = 0.77
271	(95% CI: 0.63, 1.03); p=0.09*		(95% CI: 0.60, 0.98), p=0.03*

270 \*two-sided p-value

271 The Kaplan-Meier Curve for progression for the megestrol acetate study is shown in Figure 2.

272 **Figure 2**  
 273 KAPLAN-MEIER ESTIMATES OF TIME TO PROGRESSION  
 274 (MEGESTROL ACETATE STUDY)



275

276 The results for the study comparing Femara to aminoglutethimide, with a minimum  
 277 follow-up of nine months, are shown in Table 7. (Unadjusted analyses are used.)

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**Table 7: Aminoglutethimide Study Results**

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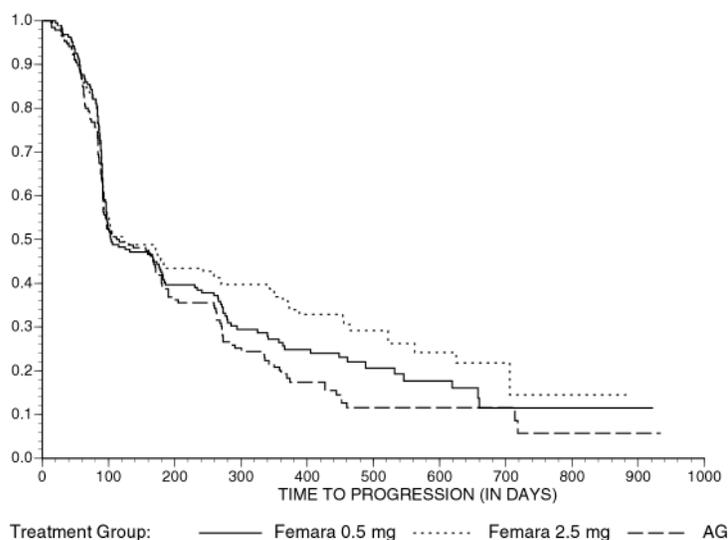
	<b>Femara® 0.5</b> <b>N = 193</b>	<b>Femara® 2.5</b> <b>N = 185</b>	<b>aminoglutethimide</b> <b>N = 179</b>
<b>Objective Response (CR + PR)</b>	34 (17.6%)	34 (18.4%)	22 (12.3%)
<b>Median Duration of Response</b>	619 days	706 days	450 days
<b>Median Time to Progression</b>	103 days	123 days	112 days
<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

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

**Figure 3**

KAPLAN-MEIER ESTIMATES OF TIME TO PROGRESSION  
(AMINOGLUTETHIMIDE STUDY)



## 307 INDICATIONS AND USAGE

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

## 312 CONTRAINDICATIONS

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

## 315 WARNINGS

### 316 Pregnancy

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

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

330 There are no studies in pregnant women. Femara<sup>®</sup> (letrozole tablets) is indicated for  
 331 post-menopausal women. If there is exposure to letrozole during pregnancy, the patient

332 should be apprised of the potential hazard to the fetus and potential risk for loss of the  
333 pregnancy.

## 334 **PRECAUTIONS**

### 335 **Laboratory Tests**

336 No dose-related effect of Femara<sup>®</sup> (letrozole tablets) on any hematologic or clinical chemistry  
337 parameter was evident. Moderate decreases in lymphocyte counts, of uncertain clinical  
338 significance, were observed in some patients receiving Femara 2.5 mg. This depression was  
339 transient in about half of those affected. Two patients on Femara developed  
340 thrombocytopenia; relationship to the study drug was unclear. Patient withdrawal due to  
341 laboratory abnormalities, whether related to study treatment or not, was infrequent.

342 Increases in SGOT, SGPT, and gamma GT  $\geq 5$  times the upper limit of normal (ULN)  
343 and of bilirubin  $\geq 1.5$  times the ULN were most often associated with metastatic disease in the  
344 liver. About 3% of study participants receiving Femara had abnormalities in liver chemistries  
345 not associated with documented metastases; these abnormalities may have been related to  
346 study drug therapy. In the megestrol acetate comparative study about 8% of patients treated  
347 with megestrol acetate had abnormalities in liver chemistries that were not associated with  
348 documented liver metastases; in the aminoglutethimide study about 10% of  
349 aminoglutethimide-treated patients had abnormalities in liver chemistries not associated with  
350 hepatic metastases.

### 351 **Drug Interactions**

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

355 Co-administration of Femara and tamoxifen 20 mg daily resulted in a reduction of letrozole  
356 plasma levels by 38% on average. There is no clinical experience to date on the use of Femara  
357 in combination with other anticancer agents.

### 358 **Hepatic Insufficiency**

359 Subjects with cirrhosis and severe hepatic dysfunction (see SPECIAL POPULATIONS) who  
360 were dosed with 2.5 mg of Femara experienced approximately twice the exposure to letrozole  
361 as healthy volunteers with normal liver function. Therefore, a dose reduction is recommended  
362 for this patient population. The effect of hepatic impairment on Femara exposure in cancer  
363 patients with elevated bilirubin levels has not been determined. (see DOSAGE &  
364 ADMINISTRATION)

### 365 **Drug/Laboratory Test-Interactions**

366 None observed.

### 367 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

368 A conventional carcinogenesis study in mice at doses of 0.6 to 60 mg/kg/day (about one to  
369 100 times the daily maximum recommended human dose on a mg/m<sup>2</sup> basis) administered by

370 oral gavage for up to 2 years revealed a dose-related increase in the incidence of benign  
371 ovarian stromal tumors. The incidence of combined hepatocellular adenoma and carcinoma  
372 showed a significant trend in females when the high dose group was excluded due to low  
373 survival. In a separate study, plasma AUC<sub>0-12hr</sub> levels in mice at 60 mg/kg/day were 55 times  
374 higher than the AUC<sub>0-24hr</sub> level in breast cancer patients at the recommended dose. The  
375 carcinogenicity study in rats at oral doses of 0.1 to 10 mg/kg/day (about 0.4 to 40 times the  
376 daily maximum recommended human dose on a mg/m<sup>2</sup> basis) for up to 2 years also produced  
377 an increase in the incidence of benign ovarian stromal tumors at 10 mg/kg/day. Ovarian  
378 hyperplasia was observed in females at doses equal to or greater than 0.1 mg/kg/day. At 10  
379 mg/kg/day, plasma AUC<sub>0-24hr</sub> levels in rats were 80 times higher than the level in breast cancer  
380 patients at the recommended dose.

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

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

## 389 **Pregnancy**

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

## 391 **Nursing Mothers**

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

## 395 **Pediatric Use**

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

## 397 **Geriatric Use**

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

402

## 403 **ADVERSE REACTIONS**

404 Femara<sup>®</sup> (letrozole tablets) was generally well tolerated across all studies as first-line and  
405 second-line treatment for breast cancer and adverse reaction rates were similar in both  
406 settings.

## 407 **First-Line Breast Cancer**

408 A total of 455 patients was treated for a median time of exposure of 11 months. The incidence  
 409 of adverse experiences was similar for Femara and tamoxifen. The most frequently reported  
 410 adverse experiences were bone pain, hot flushes, back pain, nausea, arthralgia and dyspnea.  
 411 Discontinuations for adverse experiences other than progression of tumor occurred in  
 412 10/455 (2%) of patients on Femara and in 15/455 (3%) of patients on tamoxifen.

413 Adverse events, regardless of relationship to study drug, that were reported in at least  
 414 5% of the patients treated with Femara 2.5 mg or tamoxifen 20 mg in the first-line treatment  
 415 study are shown in Table 8.

416 **Table 8: Percentage (%) of Patients with Adverse Events**

417 <b>Adverse</b>	<b>Femara®</b>	<b>tamoxifen</b>
418 <b>Experience</b>	<b>2.5 mg</b>	<b>20 mg</b>
419	<b>(n=455)</b>	<b>(n=455)</b>
420	<b>%</b>	<b>%</b>
421 <b>Body as a Whole</b>		
422 Fatigue	11	11
423 Chest pain	8	8
424 Weight decreased	6	4
425 Pain-not otherwise specified	5	6
426 Weakness	5	3
427 <b>Cardiovascular</b>		
428 Hot flushes	18	15
429 Edema-lower limb	5	5
430 Hypertension	5	4
431 <b>Digestive System</b>		
432 Nausea	15	16
433 Constipation	9	9
434 Diarrhea	7	4
435 Vomiting	7	7
436 Appetite decreased	4	6
437 Pain-abdominal	4	5
438 <b>Infections/Infestations</b>		
439 Influenza	5	4
440 <b>Musculoskeletal System</b>		
441 Pain-bone	20	18
442 Pain-back	17	17
443 Arthralgia	14	13
444 Pain-limb	8	7
445 <b>Nervous System</b>		
446 Headache	8	7
447 Insomnia	6	4
448 <b>Reproductive</b>		
449 Breast Pain	5	6
450 <b>Respiratory System</b>		
451 Dyspnea	14	15
452 Coughing	11	10
453 <b>Skin and Appendages</b>		
454 Alopecia/hair thinning	5	4
455 <b>Surgical/Medical Procedures</b>		
456 Post-mastectomy lymphoedema	7	6

457 Other less frequent ( $\leq 2\%$ ) adverse experiences considered consequential for both  
 458 treatment groups, included peripheral thromboembolic events, cardiovascular events, and

459 cerebrovascular events. Peripheral thromboembolic events included venous thrombosis,  
 460 thrombophlebitis, portal vein thrombosis and pulmonary embolism. Cardiovascular events  
 461 included angina, myocardial infarction, myocardial ischemia, and coronary heart disease.  
 462 Cerebrovascular events included transient ischemic attacks, thrombotic or hemorrhagic  
 463 strokes and development of hemiparesis.

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

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

466 Study discontinuations in the megestrol acetate comparison study for adverse events  
 467 other than progression of tumor occurred in 5/188 (2.7%) of patients on Femara 0.5 mg, in  
 468 4/174 (2.3%) of the patients on Femara 2.5 mg, and in 15/190 (7.9%) of patients on megestrol  
 469 acetate. There were fewer thromboembolic events at both Femara doses than on the megestrol  
 470 acetate arm (2 of 362 patients or 0.6% vs. 9 of 190 patients or 4.7%). There was also less  
 471 vaginal bleeding (1 of 362 patients or 0.3% vs. 6 of 190 patients or 3.2%) on letrozole than on  
 472 megestrol acetate. In the aminoglutethimide comparison study, discontinuations for reasons  
 473 other than progression occurred in 6/193 (3.1%) of patients on 0.5 mg Femara, 7/185 (3.8%)  
 474 of patients on 2.5 mg Femara, and 7/178 (3.9%) of patients on aminoglutethimide.

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

480 Adverse events, regardless of relationship to study drug, that were reported in at least  
 481 5% of the patients treated with Femara 0.5 mg, Femara 2.5 mg, megestrol acetate, or  
 482 aminoglutethimide in the two controlled trials are shown in Table 9.

483 **Table 9: Percentage (%) of Patients with Adverse Events**

484 <b>Adverse</b>	<b>Pooled</b>	<b>Pooled</b>	<b>megestrol</b>	
485 <b>Experience</b>	<b>Femara®</b>	<b>Femara®</b>	<b>acetate</b>	<b>aminoglutethimide</b>
486	<b>2.5 mg</b>	<b>0.5 mg</b>	<b>160 mg</b>	<b>500 mg</b>
487	<b>(n=359)</b>	<b>(n=380)</b>	<b>(n=189)</b>	<b>(n=178)</b>
488	<b>%</b>	<b>%</b>	<b>%</b>	<b>%</b>
489 <b>Body as a Whole</b>				
490 Fatigue	8	6	11	3
491 Chest pain	6	3	7	3
492 Peripheral edema <sup>1</sup>	5	5	8	3
493 Asthenia	4	5	4	5
494 Weight increase	2	2	9	3
495 <b>Cardiovascular</b>				
496 Hypertension	5	7	5	6
497 <b>Digestive System</b>				
498 Nausea	13	15	9	14
499 Vomiting	7	7	5	9
500 Constipation	6	7	9	7
501 Diarrhea	6	5	3	4
502 Pain-abdominal	6	5	9	8
503 Anorexia	5	3	5	5
504 Dyspepsia	3	4	6	5
505 <b>Infections/Infestations</b>				

506	Viral infection	6	5	6	3
507	<b>Lab Abnormality</b>				
508	Hypercholesterolemia	3	3	0	6
509	<b>Musculoskeletal System</b>				
510	Musculoskeletal <sup>2</sup>	21	22	30	14
511	Arthralgia	8	8	8	3
512	<b>Nervous System</b>				
513	Headache	9	12	9	7
514	Somnolence	3	2	2	9
515	Dizziness	3	5	7	3
516	<b>Respiratory System</b>				
517	Dyspnea	7	9	16	5
518	Coughing	6	5	7	5
519	<b>Skin and Appendages</b>				
520	Hot flushes	6	5	4	3
521	Rash <sup>3</sup>	5	4	3	12
522	Pruritus	1	2	5	3

523

524 <sup>1</sup> Includes peripheral edema, leg edema, dependent edema, edema525 <sup>2</sup> Includes musculoskeletal pain, skeletal pain, back pain, arm pain, leg pain526 <sup>3</sup> Includes rash, erythematous rash, maculopapular rash, psoriaform rash, vesicular rash

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

## 530 OVERDOSAGE

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

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

## 544 DOSAGE AND ADMINISTRATION

### 545 Adult and Elderly Patients

546 The recommended dose of Femara<sup>®</sup> (letrozole tablets) is one 2.5 mg tablet administered once  
 547 a day, without regard to meals. Treatment with Femara should continue until tumor  
 548 progression is evident. No dose adjustment is required for elderly patients. Patients treated  
 549 with Femara do not require glucocorticoid or mineralocorticoid replacement therapy.

550 **Renal Impairment**

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

553 **Hepatic Impairment**

554 No dosage adjustment is recommended for patients with mild-to-moderate hepatic  
555 impairment, although letrozole blood concentrations were modestly increased in subjects with  
556 moderate hepatic impairment due to cirrhosis. The dose of letrozole in patients with cirrhosis  
557 and **severe** hepatic dysfunction should be reduced by 50% (see CLINICAL  
558 PHARMACOLOGY). The recommended dose of Femara (letrozole tablets) for such patients  
559 is 2.5 mg administered every other day., The effect of hepatic impairment on Femara exposure  
560 in noncirrhotic cancer patients with elevated bilirubin levels has not been determined. (see  
561 CLINICAL PHARMACOLOGY).

562 **HOW SUPPLIED**

563 2.5 mg tablets - dark yellow, film-coated, round, slightly biconvex, with beveled edges  
564 (imprinted with the letters FV on one side and CG on the other side).

565 Packaged in HDPE bottles with a safety screw cap.

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

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

569

570 REV: AUGUST 2002

Printed in U.S.A.

T2002-XX  
XXXXXXXXXX571  **NOVARTIS**

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573 East Hanover, New Jersey 07936© 2001 Novartis  
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