HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Femara safely and effectively. See full prescribing information for Femara.

Femara (letrozole) tablets
Initial U.S. Approval: 1997

----------RECENT MAJOR CHANGES----------

Indications and Usage, Extended Adjuvant Treatment of Early Breast Cancer (1.2)	02/2008
Contraindications (4)	02/2008

----------INDICATIONS AND USAGE----------

Femara is an aromatase inhibitor indicated for:

- Adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer (1.1)
- Extended adjuvant treatment of postmenopausal women with early breast cancer who have received prior standard adjuvant tamoxifen therapy (1.2)
- First and second-line treatment of postmenopausal women with hormone receptor positive or unknown advanced breast cancer (1.3)

----------DOSAGE AND ADMINISTRATION----------

Femara tablets are taken orally without regard to meals (2):

- Recommended dose: 2.5.mg once daily (2.1)
- Patients with cirrhosis or severe hepatic impairment: 2.5 mg every other day (2.5, 5.3)

----------DOSAGE FORMS AND STRENGTHS----------

2.5 milligram tablets (3)

----------CONTRAINDICATIONS----------

Women of premenopausal endocrine status, including pregnant women (4)

----------WARNINGS AND PRECAUTIONS----------

- Decreases in bone mineral density may occur. Consider bone mineral density monitoring (5.1)
- Increases in total cholesterol may occur. Consider cholesterol monitoring. (5.2)
- Fatigue, dizziness and somnolence may occur. Exercise caution when operating machinery (5.4)

----------ADVERSE REACTIONS----------

The most common adverse reactions (>20%) were hot flashes, arthralgia (6.1); flushing, asthenia, edema, arthralgia, headache, dizziness, hypercholesterolemia, sweating increased, bone pain (6.2, 6.3); and musculoskeletal (6.4).

To report SUSPECTED ADVERSE REACTIONS, contact NOVARTIS PHARMACEUTICALS CORPORATION at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 02/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Adjuvant Treatment of Early Breast Cancer

Femara (letrozole) is indicated for the adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer. The effectiveness of Femara in early breast cancer is based on an analysis of disease-free survival in patients treated for a median of 24 months and followed for a median of 26 months [*see Clinical Studies (14.1)*]. Follow up analyses will determine long-term outcomes for both safety and efficacy.

1.2 Extended Adjuvant Treatment of Early Breast Cancer

Femara is indicated for the extended adjuvant treatment of early breast cancer in postmenopausal women, who have received 5 years of adjuvant tamoxifen therapy. The effectiveness of Femara in extended adjuvant treatment of early breast cancer is based on an analysis of disease-free survival in patients treated with Femara for a median of 60 months [*see Clinical Studies (14.2, 14.3)*].

1.3 First and Second-Line Treatment of Advanced Breast Cancer

Femara is indicated for first-line treatment of postmenopausal women with hormone receptor positive or unknown, locally advanced or metastatic breast cancer. Femara is also indicated for the treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy [*see Clinical Studies (14.4, 14.5)*].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dose of Femara is one 2.5 mg tablet administered once a day, without regard to meals.

2.2 Use in Adjuvant Treatment of Early Breast Cancer

In the adjuvant setting, the optimal duration of treatment with letrozole is unknown. The planned duration of treatment in the study was 5 years. However, at the time of analysis, the median duration of treatment was 24 months, median duration of follow-up was 26 months, and 16% of the patients had been treated for 5 years. Treatment should be discontinued at relapse [*see Clinical Studies (14.1)*].

2.3 Use in Extended Adjuvant Treatment of Early Breast Cancer

In the extended adjuvant setting, the optimal treatment duration with Femara is not known. The planned duration of treatment in the study was 5 years. The final updated analysis at a median follow-up of 62 months, the median treatment duration was 60 months, 71% of patients were treated for at least 3 years and 58% of patients completed at least 4.5 years of extended adjuvant treatment. The treatment should be discontinued at tumor relapse [*see Clinical Studies (14.2)*].

2.4 Use in First and Second-Line Treatment of Advanced Breast Cancer

In patients with advanced disease, treatment with Femara should continue until tumor progression is evident. [*see Clinical Studies (14.4, 14.5)*]

2.5 Use in Hepatic Impairment

No dosage adjustment is recommended for patients with mild to moderate hepatic impairment, although Femara blood concentrations were modestly increased in subjects with moderate hepatic impairment due to cirrhosis. The dose of Femara in patients with cirrhosis and severe hepatic dysfunction should be reduced by 50% [*see Warnings and Precautions (5.3)*]. The recommended dose of Femara for such patients is 2.5 mg administered every other day. The effect of hepatic impairment on Femara exposure in noncirrhotic cancer patients with elevated bilirubin levels has not been determined.

2.6 Use in Renal Impairment

No dosage adjustment is required for patients with renal impairment if creatinine clearance is ≥10 mL/min. [*see Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

Femara may cause fetal harm when administered to a pregnant woman and offers no clinical benefit to premenopausal women with breast cancer. Femara is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. [*see Use in Specific Populations (8.1)*]

5 WARNINGS AND PRECAUTIONS

5.1 Bone Effects

Use of Femara may cause decreases in bone mineral density (BMD). Consideration should be given to monitoring BMD. Updated results from the BMD sub-study demonstrated that at 2 years patients receiving letrozole had a median decrease from baseline of 3.8% in hip BMD compared to a median decrease of 2.0% in the placebo group. The changes from baseline in lumbar spine BMD in letrozole and placebo treated groups were not statistically different. [*see Adverse Reactions (6.2)*].

5.2 Cholesterol

Consideration should be given to monitoring serum cholesterol. In the adjuvant setting, an increase of ≥1.5 X ULN in total cholesterol (generally non-fasting) was observed in patients who had baseline total serum cholesterol within the normal range in 151/1843 (8.2%) on letrozole vs 57/1840 (3.2%) on tamoxifen. Lipid lowering medications were required for 25% of patients on letrozole and 16% on tamoxifen.

5.3 Hepatic Impairment

Subjects with cirrhosis and severe hepatic impairment who were dosed with 2.5 mg of Femara experienced approximately twice the exposure to Femara as healthy volunteers with normal liver function. Therefore, a dose reduction is recommended for this patient population. The effect of hepatic impairment on Femara exposure in cancer patients with elevated bilirubin levels has not been determined. [*see Dosage and Administration (2.5)*].

5.4 Fatigue and Dizziness

Because fatigue, dizziness, and somnolence have been reported with the use of Femara, caution is advised when driving or using machinery until it is known how the patient reacts to Femara use.

5.5 Laboratory Test Abnormalities

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

6 ADVERSE REACTIONS

The most serious adverse reactions from the use of Femara are:

- Bone effects [*see Warnings and Precautions (5.1)*]
- Increases in cholesterol [*see Warnings and Precautions (5.2)*]

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

6.1 Adjuvant Treatment of Early Breast Cancer

The median duration of adjuvant treatment was 24 months and the median duration of follow-up for safety was 26 months for patients receiving Femara and tamoxifen.

Certain adverse reactions were prospectively specified for analysis, based on the known pharmacologic properties and side effect profiles of the two drugs.

Adverse reactions were analyzed irrespective of whether a symptom was present or absent at baseline. Most adverse reactions reported (82%) were Grade 1 and Grade 2 applying the Common Toxicity Criteria Version 2.0. Table 1 describes adverse reactions (Grades 1-4) irrespective of relationship to study treatment in the adjuvant trial (safety population, during treatment or within 30 days of stopping treatment).

Table 1: Patients with Adverse Reactions (CTC Grades 1-4, Irrespective of Relationship to Study Drug) in the Adjuvant Study

	Grades 1-4				**Grades 3-4**			
Adverse Reaction	**Femara N=3975 n (%)**		**tamoxifen N=3988 n (%)**		**Femara N=3975 n (%)**		**tamoxifen N=3988 n (%)**	
Hot Flashes/Flushes	1338	(33.7)	1515	(38)	0	-	0	-
Arthralgia/Arthritis	840	(21.1)	535	(13.4)	88	(2.2)	49	(1.2)
Night Sweats	561	(14.1)	654	(16.4)	0	-	0	-
Weight Increase	425	(10.7)	515	(12.9)	21	(0.5)	44	(1.1)
Nausea	378	(9.5)	416	(10.4)	6	(0.2)	10	(0.3)
Fatigue (Lethargy, Malaise, Asthenia)	333	(8.4)	345	(8.7)	9	(0.2)	9	(0.2)
Edema	286	(7.2)	287	(7.2)	5	(0.1)	2	(<0.1)
Myalgia	255	(6.4)	243	(6.1)	26	(0.7)	17	(0.4)
Bone Fractures	223	(5.6)	158	(4.0)	76	(1.9)	45	(1.1)
Vaginal Bleeding	177	(4.5)	411	(10.3)	2	(<0.1)	7	(0.2)
Headache	141	(3.5)	126	(3.2)	12	(0.3)	6	(0.2)
Vaginal Irritation	139	(3.5)	122	(3.1)	6	(0.2)	3	(<0.1)
Vomiting	109	(2.7)	106	(2.7)	6	(0.2)	8	(0.2)
Dizziness/Light-Headedness	96	(2.4)	110	(2.8)	1	(<0.1)	8	(0.2)
Osteoporosis	79	(2)	44	(1.1)	6	(0.2)	7	(0.2)
Constipation	59	(1.5)	95	(2.4)	4	(0.1)	1	(<0.1)
Endometrial Proliferation Disorders	10	(0.3)	71	(1.8)	1	(<0.1)	12	(0.3)
Endometrial Cancer [1]	7/3089	(0.2)	12/3157	(0.4)	-	-	-	-
Other Endometrial Disorders	3	(<0.1)	4	(0.1)	0	-	1	(<0.1)
Myocardial Infarction	17	(0.4)	14	(0.4)	15	(0.4)	11	(0.3)
Cerebrovascular/TIA	44	(1.1)	41	(1.0)	43	(1.1)	40	(1)
Angina	27	(0.7)	24	(0.6)	17	(0.4)	7	(0.2)
Thromboembolic Event	44	(1.1)	109	(2.7)	29	(0.7)	79	(2)
Other Cardiovascular	261	(6.6)	248	(6.2)	97	(2.4)	71	(1.8)
Second Malignancies [2]	76/4003	(1.9)	96/4007	(2.4)	-	-	-	-

[1] Based on safety population excluding patients who had undergone hysterectomy; time frame is any time after randomization; no CTC grades collected (yes/no response)

[2] Based on the intent-to-treat population; time frame is any time after randomization; no CTC grades collected (yes/no response)

When considering all grades, a higher incidence of events were seen for Femara regarding fractures (5.7% vs 4%), myocardial infarctions (0.6% vs 0.4%), and arthralgia (21.2% vs 13.5%) (Femara vs tamoxifen respectively). A higher incidence was seen for tamoxifen regarding thromboembolic events (1.2% vs 2.8%), endometrial cancer (0.2% vs 0.4%), and endometrial proliferative disorders (0.3% vs 1.8%) (Femara vs tamoxifen respectively).

6.2 Extended Adjuvant Treatment of Early Breast Cancer, Median Treatment Duration of 24 Months

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

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

Table 2: Percentage of Patients with Adverse Reactions

	Number (%) of Patients with Grade 1-4 Adverse Reaction		**Number (%) of Patients with Grade 3-4 Adverse Reaction**	
	Femara N=2563	**Placebo N=2573**	**Femara N=2563**	**Placebo N=2573**
Any Adverse Reaction	2232 (87.1)	2174 (84.5)	419 (16.3)	389 (15.1)
Vascular Disorders	1375 (53.6)	1230 (47.8)	59 (2.3)	74 (2.9)
Flushing	1273 (49.7)	1114 (43.3)	3 (0.1)	0 -
General Disorders	1154 (45)	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)
Musculoskeletal Disorders	978 (38.2)	836 (32.5)	71 (2.8)	50 (1.9)
Arthralgia	565 (22)	465 (18.1)	25 (1)	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)	112 (4.4)	8 (0.3)	7 (0.3)
Nervous System Disorders	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)
Skin Disorders	830 (32.4)	787 (30.6)	17 (0.7)	16 (0.6)
Sweating Increased	619 (24.2)	577 (22.4)	1 (<0.1)	0 -
Gastrointestinal Disorders	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)	143 (5.6)	12 (0.5)	8 (0.3)
Metabolic Disorders	551 (21.5)	537 (20.9)	24 (0.9)	32 (1.2)
Hypercholesterolemia	401 (15.6)	398 (15.5)	2 (<0.1)	5 (0.2)
Reproductive Disorders	303 (11.8)	357 (13.9)	9 (0.4)	8 (0.3)
Vaginal Hemorrhage	123 (4.8)	171 (6.6)	2 (<0.1)	5 (0.2)
Vulvovaginal Dryness	137 (5.3)	127 (4.9)	0 -	0 -
Psychiatric Disorders	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)
Respiratory Disorders	279 (10.9)	260 (10.1)	30 (1.2)	28 (1.1)
Dyspnea	140 (5.5)	137 (5.3)	21 (0.8)	18 (0.7)

Investigations	184 (7.2)	147 (5.7)	13 (0.5)	13 (0.5)
Infections and Infestations	166 (6.5)	163 (6.3)	40 (1.6)	33 (1.3)
Renal Disorders	130 (5.1)	100 (3.9)	12 (0.5)	6 (0.2)

Based on a median follow-up of patients for 28 months, the incidence of clinical fractures from the core randomized study in patients who received Femara was 5.9% (152) and placebo was 5.5% (142). The incidence of self-reported osteoporosis was higher in patients who received Femara 6.9% (176) than in patients who received placebo 5.5% (141). Bisphosphonates were administered to 21.1% of the patients who received Femara and 18.7% of the patients who received placebo.

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

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

***Bone Sub-study*:** [*see Warnings and Precautions (5.1)*].

Lipid Sub-study: Based on a median duration of follow-up of 62 months for Femara, there was no significant difference between Femara and placebo in total cholesterol or in any lipid fraction at any time over 5 years. Use of lipid lowering drugs or dietary management of elevated lipids was allowed. [*see Warnings and Precautions (5.2)*]

6.3 Updated Analysis, Extended Adjuvant Treatment of Early Breast Cancer, Median Treatment Duration of 60 Months

The extended adjuvant treatment trial was unblinded early [*see Adverse Reactions (6.2)*]. At the updated (final analysis), overall the side effects seen were consistent to those seen at a median treatment duration of 24 months.

6.4 First-Line Treatment of Advanced Breast Cancer

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

Adverse reactions, regardless of relationship to study drug, that were reported in at least 5% of the patients treated with Femara 2.5 mg or tamoxifen 20 mg in the first-line treatment study are shown in Table 3.

Table 3: Percentage (%) of Patients with Adverse Reactions

Adverse Reaction	**Femara 2.5 mg (N=455) %**	**tamoxifen 20 mg (N=455) %**
General Disorders		
Fatigue	13	13
Chest Pain	8	9
Edema Peripheral	5	6
Pain NOS	5	7
Weakness	6	4
Investigations		
Weight Decreased	7	5
Vascular Disorders		
Hot Flushes	19	16

Hypertension	8	4
Gastrointestinal Disorders		
Nausea	17	17
Constipation	10	11
Diarrhea	8	4
Vomiting	7	8
Infections/Infestations		
Influenza	6	4
Urinary Tract Infection NOS	6	3
Injury, Poisoning and Procedural Complications		
Post-Mastectomy Lymphedema	7	7
Metabolism and Nutrition Disorders		
Anorexia	4	6
Musculoskeletal and Connective Tissue Disorders		
Bone Pain	22	21
Back Pain	18	19
Arthralgia	16	15
Pain in Limb	10	8
Nervous System Disorders		
Headache NOS	8	7
Psychiatric Disorders		
Insomnia	7	4
Reproductive System and Breast Disorders		
Breast Pain	7	7
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	18	17
Cough	13	13
Chest Wall Pain	6	6

Other less frequent (≤2%) adverse reactions considered consequential for both treatment groups, included peripheral thromboembolic events, cardiovascular events, and cerebrovascular events. Peripheral thromboembolic events included venous thrombosis, thrombophlebitis, portal vein thrombosis and pulmonary embolism. Cardiovascular events included angina, myocardial infarction, myocardial ischemia, and coronary heart disease. Cerebrovascular events included transient ischemic attacks, thrombotic or hemorrhagic strokes and development of hemiparesis.

6.5 Second- Line Treatment of Advanced Breast Cancer

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

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

Adverse reactions, regardless of relationship to study drug, that were reported in at least 5% of the patients treated with Femara 0.5 mg, Femara 2.5 mg, megestrol acetate, or aminoglutethimide in the two controlled trials are shown in Table 4.

Table 4: Percentage (%) of Patients with Adverse Reactions

Adverse Reaction	Pooled Femara 2.5 mg (N=359) %	Pooled Femara 0.5 mg (N=380) %	megestrol acetate 160 mg (N=189) %	aminoglutethimide 500 mg (N=178) %
Body as a Whole				
Fatigue	8	6	11	3
Chest Pain	6	3	7	3
Peripheral Edema[1]	5	5	8	3
Asthenia	4	5	4	5
Weight Increase	2	2	9	3
Cardiovascular				
Hypertension	5	7	5	6
Digestive System				
Nausea	13	15	9	14
Vomiting	7	7	5	9
Constipation	6	7	9	7
Diarrhea	6	5	3	4
Pain-Abdominal	6	5	9	8
Anorexia	5	3	5	5
Dyspepsia	3	4	6	5
Infections/Infestations				
Viral Infection	6	5	6	3
Lab Abnormality				
Hypercholesterolemia	3	3	0	6
Musculoskeletal System				
Musculoskeletal[2]	21	22	30	14
Arthralgia	8	8	8	3
Nervous System				
Headache	9	12	9	7
Somnolence	3	2	2	9
Dizziness	3	5	7	3
Respiratory System				
Dyspnea	7	9	16	5
Coughing	6	5	7	5
Skin and Appendages				
Hot Flushes	6	5	4	3
Rash[3]	5	4	3	12
Pruritus	1	2	5	3

[1] Includes peripheral edema, leg edema, dependent edema, edema
[2] Includes musculoskeletal pain, skeletal pain, back pain, arm pain, leg pain
[3] Includes rash, erythematous rash, maculopapular rash, psoriasiform rash, vesicular rash

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

6.6 First and Second-Line Treatment of Advanced Breast Cancer

In the combined analysis of the first- and second-line metastatic trials and post-marketing experiences other adverse reactions that were reported were cataract, eye irritation, palpitations, cardiac failure, tachycardia, dysesthesia (including hypesthesia/paresthesia), arterial thrombosis, memory impairment, irritability, nervousness, urticaria, increased urinary frequency, leukopenia, stomatitis cancer pain, pyrexia, vaginal discharge, appetite increase, dryness of skin and mucosa (including dry mouth), and disturbances of taste and thirst.

6.7 Postmarketing Experience

Cases of blurred vision and increased hepatic enzymes, angioedema, anaphylactic reactions, toxic epidermal necrolysis, erythema multiforme and hepatitis have been reported.

7 DRUG INTERACTIONS

Tamoxifen

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

Cimetidine

A pharmacokinetic interaction study with cimetidine showed no clinically significant effect on letrozole pharmacokinetics.

Warfarin

An interaction study with warfarin showed no clinically significant effect of letrozole on warfarin pharmacokinetics.

Other Anticancer Agents

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X [*see Contraindications (4)*].

Femara may cause fetal harm when administered to a pregnant woman and offers no clinical benefit to premenopausal women with breast cancer. Femara is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Femara caused adverse pregnancy outcomes, including congenital malformations, in rats and rabbits at doses much smaller than the daily maximum recommended human dose (MRHD) on a mg/m^2 basis. Effects included increased post-implantation pregnancy loss and resorptions, fewer live fetuses, and fetal malformations affecting the renal and skeletal systems. Animal data and letrozole's mechanism of action raise concerns that letrozole could be a human teratogen as well.

Reproduction studies in rats showed embryo and fetal toxicity at letrozole doses during organogenesis equal to or greater than 1/100 the daily maximum recommended human dose (MHRD) (mg/m^2 basis). Adverse effects included: intrauterine mortality; increased resorptions and postimplantation loss; decreased numbers of live fetuses; and fetal anomalies including absence and shortening of renal papilla, dilation of ureter, edema and incomplete ossification of frontal skull and metatarsals. Letrozole doses 1/10 the daily MHRD (mg/m^2 basis)

caused fetal domed head and cervical/centrum vertebral fusion. In rabbits, letrozole caused embryo and fetal toxicity at doses about 1/100,000 and 1/10,000 the daily MHRD respectively (mg/m^2 basis). Fetal anomalies included incomplete ossification of the skull, sternebrae, and fore- and hind legs. [*see Nonclinical Toxicology (13.2)*].

Physicians should discuss the need for adequate contraception with women who are recently menopausal. Contraception should be used until postmenopausal status is clinically well established.

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

For the extended adjuvant setting, more than 5,100 postmenopausal women were enrolled in the clinical study. In total, 41% of patients were aged 65 years or older at enrollment, while 12% were 75 or older. In the extended adjuvant setting, no overall differences in safety or efficacy were observed between these older patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

In the adjuvant setting, more than 8,000 postmenopausal women were enrolled in the clinical study. In total, 36 % of patients were aged 65 years or older at enrollment, while 12% were 75 or older. More adverse reactions were generally reported in elderly patients irrespective of study treatment allocation. However, in comparison to tamoxifen, no overall differences with regards to the safety and efficacy profiles were observed between elderly patients and younger patients.

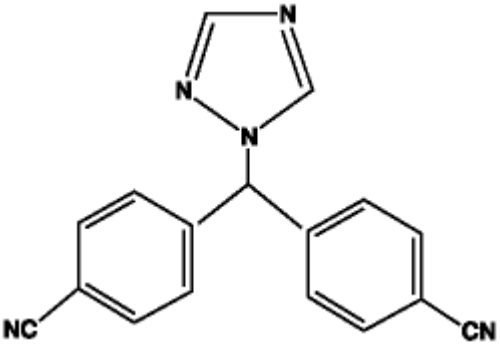
10 OVERDOSAGE

Isolated cases of Femara overdose have been reported. In these instances, the highest single dose ingested was 62.5 mg or 25 tablets. While no serious adverse reactions were reported in these cases, because of the limited data available, no firm recommendations for treatment can be made. However, emesis could be induced if the patient is alert. In general, supportive care and frequent monitoring of vital signs are also appropriate. In single-dose studies, the highest dose used was 30 mg, which was well tolerated; in multiple-dose trials, the largest dose of 10 mg was well tolerated.

Lethality was observed in mice and rats following single oral doses that were equal to or greater than 2,000 mg/kg (about 4,000 to 8,000 times the daily maximum recommended human dose on a mg/m^2 basis); death was associated with reduced motor activity, ataxia and dyspnea. Lethality was observed in cats following single IV doses that were equal to or greater than 10 mg/kg (about 50 times the daily maximum recommended human dose on a mg/m^2 basis); death was preceded by depressed blood pressure and arrhythmias.

11 DESCRIPTION

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



Letrozole is a white to yellowish crystalline powder, practically odorless, freely soluble in dichloromethane, slightly soluble in ethanol, and practically insoluble in water. It has a molecular weight of 285.31, empirical formula $C_{17}H_{11}N_5$, and a melting range of 184°C-185°C.

Femara is available as 2.5 mg tablets for oral administration.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The growth of some cancers of the breast is stimulated or maintained by estrogens. Treatment of breast cancer thought to be hormonally responsive (i.e., estrogen and/or progesterone receptor positive or receptor unknown) has included a variety of efforts to decrease estrogen levels (ovariectomy, adrenalectomy, hypophysectomy) or inhibit estrogen effects (antiestrogens and progestational agents). These interventions lead to decreased tumor mass or delayed progression of tumor growth in some women.

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

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

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

12.2 Pharmacodynamics

In postmenopausal patients with advanced breast cancer, daily doses of 0.1 mg to 5 mg Femara suppress plasma concentrations of estradiol, estrone, and estrone sulfate by 75%-95% from baseline with maximal suppression achieved within two-three days. Suppression is dose-related, with doses of 0.5 mg and higher giving many values of estrone and estrone sulfate that were below the limit of detection in the assays. Estrogen suppression was maintained throughout treatment in all patients treated at 0.5 mg or higher.

Letrozole is highly specific in inhibiting aromatase activity. There is no impairment of adrenal steroidogenesis. No clinically-relevant changes were found in the plasma concentrations of cortisol, aldosterone, 11-deoxycortisol, 17-hydroxy-progesterone, ACTH or in plasma renin activity among postmenopausal patients

treated with a daily dose of Femara 0.1 mg to 5 mg. The ACTH stimulation test performed after 6 and 12 weeks of treatment with daily doses of 0.1, 0.25, 0.5, 1, 2.5, and 5 mg did not indicate any attenuation of aldosterone or cortisol production. Glucocorticoid or mineralocorticoid supplementation is, therefore, not necessary.

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

12.3 Pharmacokinetics

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

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

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

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

***Renal Impairment**:* In a study of volunteers with varying renal function (24-hour creatinine clearance: 9-116 mL/min), no effect of renal function on the pharmacokinetics of single doses of 2.5 mg of Femara was found. In addition, in a study of 347 patients with advanced breast cancer, about half of whom received 2.5 mg Femara and half 0.5 mg Femara, renal impairment (calculated creatinine clearance: 20-50 mL/min) did not affect steady-state plasma letrozole concentrations.

Hepatic Impairment: In a study of subjects with mild to moderate non-metastatic hepatic dysfunction (e.g., cirrhosis, Child-Pugh classification A and B), the mean AUC values of the volunteers with moderate hepatic impairment were 37% higher than in normal subjects, but still within the range seen in subjects without impaired function.

In a pharmacokinetic study, subjects with liver cirrhosis and severe hepatic impairment (Child-Pugh classification C, which included bilirubins about 2-11 times ULN with minimal to severe ascites) had two-fold increase in exposure (AUC) and 47% reduction in systemic clearance. Breast cancer patients with severe hepatic impairment are thus expected to be exposed to higher levels of letrozole than patients with normal liver function receiving similar doses of this drug. [*see Dosage and Administration (2.5)*]

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A conventional carcinogenesis study in mice at doses of 0.6 to 60 mg/kg/day (about 1 to 100 times the daily maximum recommended human dose on a mg/m^2 basis) administered by oral gavage for up to 2 years revealed a dose-related increase in the incidence of benign ovarian stromal tumors. The incidence of combined hepatocellular adenoma and carcinoma showed a significant trend in females when the high dose group was excluded due to low survival. In a separate study, plasma $AUC_{0\text{-}12hr}$ levels in mice at 60 mg/kg/day were 55 times higher than the $AUC_{0\text{-}24hr}$ level in breast cancer patients at the recommended dose. The carcinogenicity study in rats at oral doses of 0.1 to 10 mg/kg/day (about 0.4 to 40 times the daily maximum recommended human dose on a mg/m^2 basis) for up to 2 years also produced an increase in the incidence of benign ovarian stromal tumors at 10 mg/kg/day. Ovarian hyperplasia was observed in females at doses equal to or greater than 0.1 mg/kg/day. At 10 mg/kg/day, plasma $AUC_{0\text{-}24hr}$ levels in rats were 80 times higher than the level in breast cancer patients at the recommended dose.

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

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

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology: Reproduction studies in rats at letrozole doses equal to or greater than 0.003 mg/kg (about 1/100 the daily maximum recommended human dose on a mg/m^2 basis) administered during the period of organogenesis, have shown that letrozole is embryotoxic and fetotoxic, as indicated by intrauterine mortality, increased resorption, increased postimplantation loss, decreased numbers of live fetuses and fetal anomalies including absence and shortening of renal papilla, dilation of ureter, edema and incomplete ossification of frontal skull and metatarsals. Letrozole was teratogenic in rats. A 0.03 mg/kg dose (about 1/10 the daily maximum recommended human dose on a mg/m^2 basis) caused fetal domed head and cervical/centrum vertebral fusion.

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

14 CLINICAL STUDIES

14.1 Adjuvant Treatment of Early Breast Cancer

A multicenter, double-blind study randomized over 8,000 postmenopausal women with resected, receptor-positive early breast cancer to one of the following arms:

A. tamoxifen for 5 years

B. Femara for 5 years

C. tamoxifen for 2 years followed by Femara for 3 years

D. Femara for 2 years followed by tamoxifen for 3 years

Median treatment duration was 24 months and median follow-up duration was 26 months, 76% of the patients have been followed for more than 2 years, and 16% of patients for 5 years or longer.

Data in Table 6 reflects results from non-switching arms (arms A and B) together with data truncated 30 days after the switch in the two switching arms (arms C and D). The analysis of monotherapy vs sequencing of

endocrine treatments will be conducted when the necessary number of events has been achieved. Selected baseline characteristics for the study population are shown in Table 5.

Table 5: Selected Study Population Demographics for Adjuvant Study (ITT Population)

Baseline Status	**Femara N=4003**	**tamoxifen N=4007**
Age (median, years)	61	61
Age Range (years)	38-89	39-90
Hormone Receptor Status (%)		
ER+ and/or PgR+	99.7	99.7
Both Unknown	0.3	0.3
Nodal Status (%)		
Node Negative	52	52
Node Positive	41	41
Nodal Status Unknown	7	7
Prior Adjuvant Chemotherapy (%)	25	25

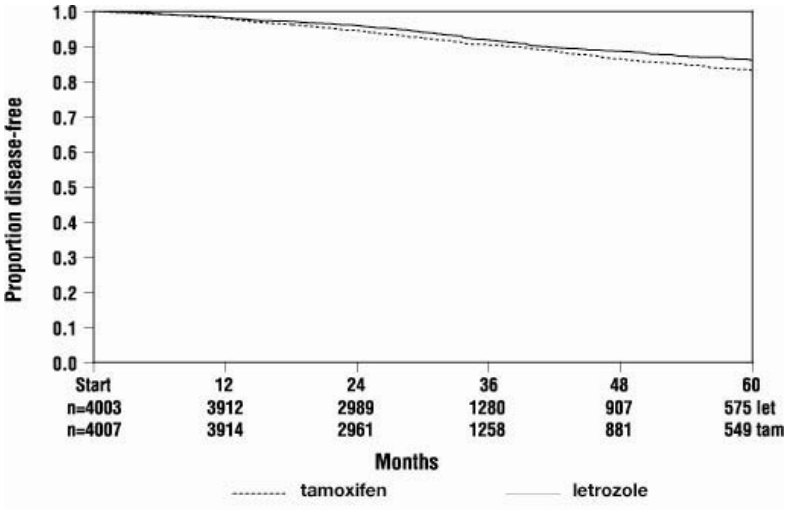
Table 6: Adjuvant Study Results*

	Femara N=4003	**tamoxifen** N=4007	**Hazard Ratio (95 % CI)**	**P-Value**
Disease-Free Survival[1]	296	369	0.79 (0.68, 0.92)	0.002
Node Positive			0.71 (0.59, 0.86)	
Node Negative			0.92 (0.70, 1.22)	
Prior Adjuvant Chemotherapy			0.70 (0.53, 0.93)	
No Chemotherapy			0.83 (0.69, 1.00)	
Systemic Disease-Free Survival[2]	268	321	0.83 (0.70, 0.97)	0.022
Time to Distant Metastasis[3]	184	249	0.73 (0.60, 0.88)	0.001
Node Positive			0.67 (0.54, 0.84)	
Node Negative			0.90 (0.60, 1.34)	
Prior Adjuvant Chemotherapy			0.69 (0.50, 0.95)	
No Chemotherapy			0.75 (0.60, 0.95)	
Distant Disease Free Survival[4]	265	318	0.82 (0.70, 0.97)	0.020
Contralateral Breast Cancer	19	31	0.61 (0.35, 1.08)	0.091
Overall Survival	166	192	0.86 (0.70, 1.06)	0.155
Node Positive			0.81 (0.63, 1.05)	
Node Negative			0.88 (0.59, 1.30)	
Prior Adjuvant Chemotherapy			0.76 (0.51, 1.14)	
No Chemotherapy			0.90 (0.71, 1.15)	

*Definition of:
[1] Disease-Free Survival: Time from randomization to the earliest occurrence of invasive loco-regional recurrence, distant metastases, invasive contralateral breast cancer, or death from any cause.
[2]Systemic Disease-Free Survival: Time from randomization to invasive regional recurrence, distant metastases, or death from any cause.
[3]Time to Distant Metastasis: Time from randomization to distant metastases.
[4] Distant Disease Free Survival: Time from randomization to the earliest recurrence of relapse to a distant site or death from any cause.

Figure 1 shows the Kaplan-Meier curves for Disease-Free Survival.

Figure 1 Disease-Free Survival (ITT Population)



14.2 Extended Adjuvant Treatment of Early Breast Cancer, Median Treatment Duration of 24 Months

A double-blind, randomized, placebo-controlled trial of Femara was performed in over 5,100 postmenopausal women with receptor-positive or unknown primary breast cancer who were disease free after 5 years of adjuvant treatment with tamoxifen.

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

Selected baseline characteristics for the study population are shown in Table 7.

Table 7: Selected Study Population Demographics (Modified ITT Population)

Baseline Status	**Femara N=2582**	**Placebo N=2586**
Hormone Receptor Status (%)		
ER+ and/or PgR+	98	98
Both Unknown	2	2
Nodal Status (%)		
Node Negative	50	50
Node Positive	46	46
Nodal Status Unknown	4	4
Chemotherapy	46	46

Table 8 shows the study results. Disease-free survival was measured as the time from randomization to the earliest event of loco-regional or distant recurrence of the primary disease or development of contralateral breast cancer or death. DFS by hormone receptor status, nodal status and adjuvant chemotherapy were similar to the overall results. Data were premature for an analysis of survival.

Table 8: Extended Adjuvant Study Results

	Femara N = 2582	**Placebo N = 2586**	**Hazard Ratio (95% CI)**	**P-Value**
Disease Free Survival (DFS)	122 (4.7%)	193 (7.5%)	0.62 (0.49, 0.78)[1]	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		

CI = confidence interval for hazard ratio. Hazard ratio of less than 1.0 indicates difference in favor of Femara (lesser risk of recurrence); hazard ratio greater than 1.0 indicates difference in favor of placebo (higher risk of recurrence with Femara).
[1] Analysis stratified by receptor status, nodal status and prior adjuvant chemotherapy (stratification factors as at randomization). P-value based on stratified logrank test.
[2] First event of loco-regional recurrence, distant relapse, contralateral breast cancer or death from any cause

14.3 Updated Analyses of Extended Adjuvant Treatment of Early Breast Cancer, Median Treatment Duration of 60 Months

Table 9: Update of Extended Adjuvant Study Results

	Femara N = 2582	**Placebo N = 2586**	**Hazard Ratio[1] (95% CI)**	***P*-Value[2]**
Disease Free Survival (DFS) events[3]	344	402	0.89 (0.77, 1.03)	0.12
Breast cancer recurrence (Protocol definition of DFS events[4])	209	286	0.75 (0.63, 0.89)	0.001
Local Breast Recurrence	15	43		
Local Chest Wall Recurrence	6	14		
Regional Recurrence	10	8		
Distant Recurrence	140	167		
Distant recurrence (first or subsequent events)	142	169	0.88 (0.70,1.10)	0.246
Contralateral Breast Cancer	37	53		
Deaths Without Recurrence or Contralateral Breast Cancer	135	116		

[1] Adjusted by receptor status, nodal status and prior chemotherapy
[2] Stratified logrank test, stratified by receptor status, nodal status and prior chemotherapy
[3] DFS events defined as earliest of loco-regional recurrence, distant metastasis, contralateral breast cancer or death from any cause, and ignoring switches to Femara in 60% of the placebo arm.
[4] Protocol definition does not include deaths from any cause

Updated analyses were conducted at a median follow-up of 62 months. In the Femara arm, 71% of patients were treated for at least 3 years and 58% of patients completed at least 4.5 years of extended adjuvant treatment. After the unblinding of the study at a median follow-up of 28 months, approximately 60% of the selected patients in the placebo arm opted to switch to Femara.

In this updated analysis shown in Table 9, Femara significantly reduced the risk of breast cancer recurrence or contralateral breast cancer compared with placebo (HR 0.75; 95% CI 0.63, 0.89; P=0.001). However, in the updated DFS analysis (interval between randomization and earliest event of loco-regional recurrence, distant metastasis, contralateral breast cancer, or death from any cause) the treatment difference was heavily diluted by 60% of the patients in the placebo arm switching to Femara and accounting for 64% of the total placebo patient-years of follow-up. Ignoring these switches, the risk of a DFS event was reduced by a non-significant 11% (HR 0.89; 95% CI 0.77, 1.03). There was also no significant difference in distant disease-free survival or overall survival.

14.4 First-Line Treatment of Advanced Breast Cancer

A randomized, double-blind, multinational trial compared Femara 2.5 mg with tamoxifen 20 mg in 916 postmenopausal patients with locally advanced (Stage IIIB or loco-regional recurrence not amenable to treatment with surgery or radiation) or metastatic breast cancer. Time to progression (TTP) was the primary endpoint of the trial. Selected baseline characteristics for this study are shown in Table 10.

Table 10: Selected Study Population Demographics

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

Femara was superior to tamoxifen in TTP and rate of objective tumor response (see Table 10).

Table 11 summarizes the results of the trial, with a total median follow-up of approximately 32 months. (All analyses are unadjusted and use 2-sided P-values.)

Table 11: Results of First-Line Treatment of Advanced Breast Cancer

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

[1] Hazard ratio
[2] Odds ratio
[3] Overall logrank test

Figure 2 shows the Kaplan-Meier curves for TTP.

Figure 2 Kaplan-Meier Estimates of Time to Progression (Tamoxifen Study)

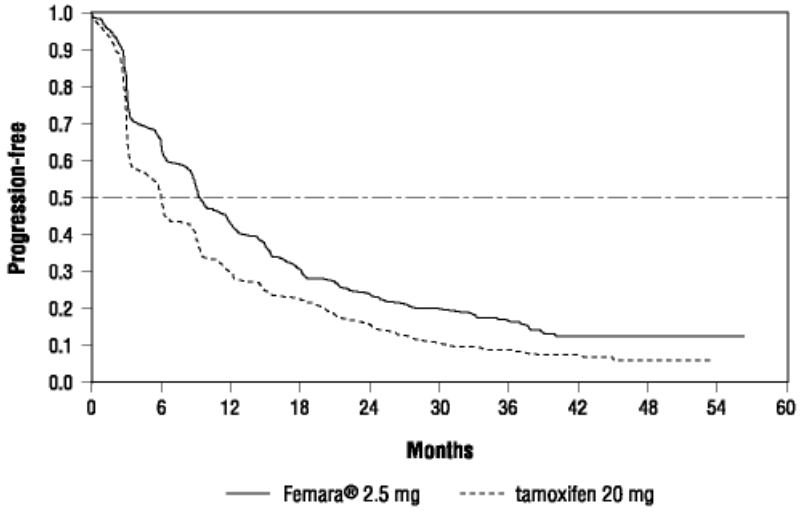


Table 12 shows results in the subgroup of women who had received prior antiestrogen adjuvant therapy, Table 13, results by disease site and Table 14, the results by receptor status.

Table 12: Efficacy in Patients Who Received Prior Antiestrogen Therapy

Variable	Femara 2.5 mg N=84	tamoxifen 20 mg N=83
Median Time to Progression (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)	
Objective Response Rate		
(CR + PR)	22 (26%)	7 (8%)
Odds Ratio for Response (95% CI)	3.85 (1.50, 9.60)	

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

Table 13: Efficacy by Disease Site

	Femara 2.5 mg	tamoxifen 20 mg
Dominant Disease Site		
Soft Tissue:	N=113	N=115
Median TTP	12.1 months	6.4 months
Objective Response Rate	50%	34%
Bone:	N=145	N=131
Median TTP	9.5 months	6.3 months
Objective Response Rate	23%	15%
Viscera:	N=195	N=208
Median TTP	8.3 months	4.6 months
Objective Response Rate	28%	17%

Table 14: Efficacy by Receptor Status

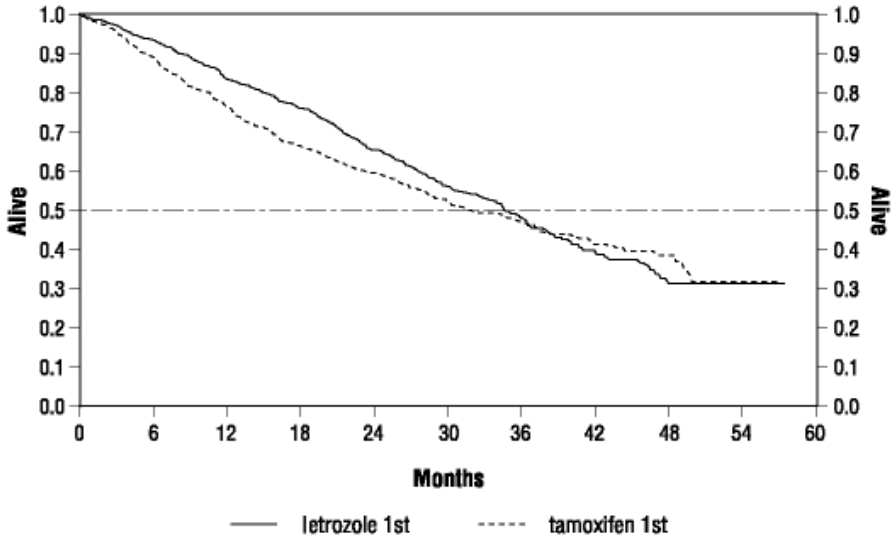
Variable	Femara 2.5 mg	tamoxifen 20 mg
Receptor Positive	N=294	N=305
Median Time to Progression (95% CI)	9.4 months (8.9, 11.8)	6.0 months (5.1, 8.5)
Hazard Ratio for TTP (95% CI)	0.69 (0.58, 0.83)	
Objective Response Rate (CR+PR)	97 (33%)	66 (22%)
Odds Ratio for Response 95% CI)	1.78 (1.20, 2.60)	

Receptor Unknown	N=159	N=149
Median Time to Progression (95% CI)	9.2 months (6.1, 12.3)	6.0 months (4.1, 6.4)
Hazard Ratio for TTP (95% CI)	0.77 (0.60, 0.99)	
Objective Response Rate (CR+PR)	48 (30%)	29 (20%)
Odds Ratio for Response (95% CI)	1.79 (1.10, 3.00)	

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

Figure 3 shows the Kaplan-Meier curves for survival.

Figure 3 Survival by Randomized Treatment Arm



Legend: Randomized Femara: 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).

The median overall survival was 35 months for the Femara group and 32 months for the tamoxifen group, with a P-value 0.5136. Study design allowed patients to cross over 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 cross over to the opposite treatment arm, median survival was 35 months with Femara (n=219, 95% Cl 29 to 43 months) vs 20 months with tamoxifen (n=229, 95% Cl 16 to 26 months).

14.5 Second-Line Treatment of Advanced Breast Cancer

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 antiestrogen 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).

Two large randomized, controlled, multinational (predominantly European) trials were conducted in patients with advanced breast cancer who had progressed despite antiestrogen therapy. Patients were randomized to Femara 0.5 mg daily, Femara 2.5 mg daily, or a comparator (megestrol acetate 160 mg daily in one study; and aminoglutethimide 250 mg b.i.d. with corticosteroid supplementation in the other study). In each study over

60% of the patients had received therapeutic antiestrogens, and about one-fifth of these patients had had an objective response. The megestrol acetate controlled study was double-blind; the other study was open label. Selected baseline characteristics for each study are shown in Table 15.

Table 15: Selected Study Population Demographics

Parameter	megestrol acetate study	aminoglutethimide study
No. of Participants	552	557
Receptor Status		
ER/PR Positive	57%	56%
ER/PR Unknown	43%	44%
Previous Therapy		
Adjuvant Only	33%	38%
Therapeutic +/- Adj.	66%	62%
Sites of Disease		
Soft Tissue	56%	50%
Bone	50%	55%
Viscera	40%	44%

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

Table 16 shows the results for the first trial, with a minimum follow-up of 15 months, that compared Femara 0.5 mg, Femara 2.5 mg, and megestrol acetate 160 mg daily. (All analyses are unadjusted.)

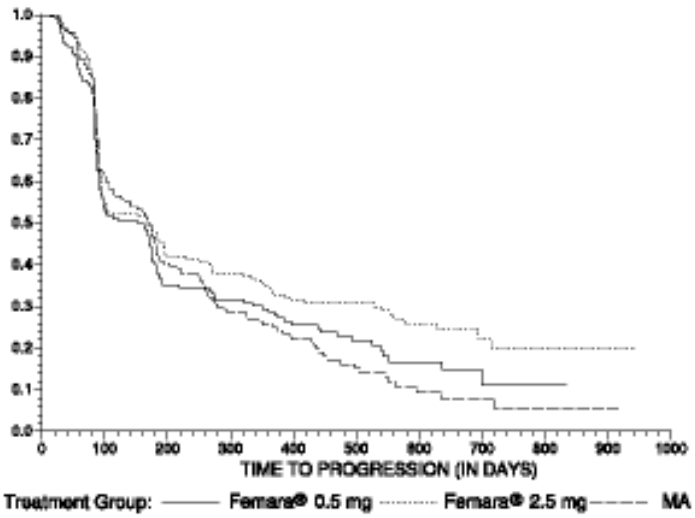
Table 16: Megestrol Acetate Study Results

	Femara 0.5 mg N=188	Femara 2.5 mg N=174	megestrol acetate N=190
Objective Response (CR + PR)	22 (11.7%)	41 (23.6%)	31 (16.3%)
Median Duration of Response	552 days	(Not reached)	561 days
Median Time to Progression	154 days	170 days	168 days
Median Survival	633 days	730 days	659 days
Odds Ratio for Response	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*
Relative Risk of Progression	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

The Kaplan-Meier curves for progression for the megestrol acetate study are shown in Figure 4.

Figure 4 Kaplan-Meier Estimates of Time to Progression (Megestrol Acetate Study)



The results for the study comparing Femara to aminoglutethimide, with a minimum follow-up of 9 months, are shown in Table 17. (Unadjusted analyses are used.)

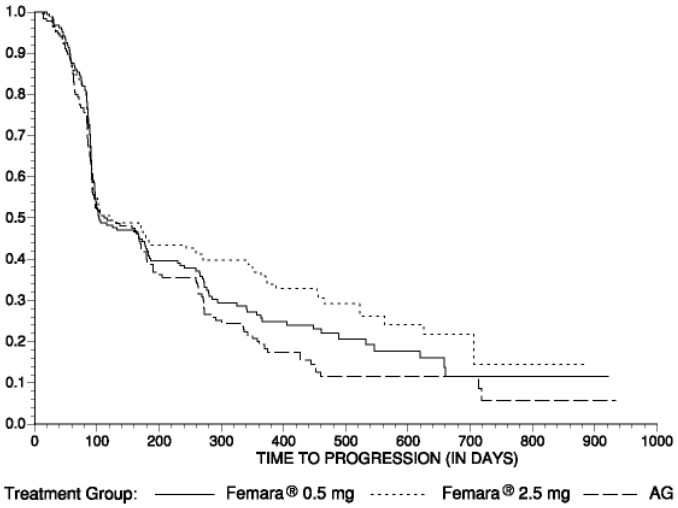
Table 17: Aminoglutethimide Study Results

	Femara 0.5 mg N=193	**Femara 2.5 mg N=185**	**aminoglutethimide N=179**
Objective Response (CR + PR)	34 (17.6%)	34 (18.4%)	22 (12.3%)
Median Duration of Response	619 days	706 days	450 days
Median Time to Progression	103 days	123 days	112 days
Median Survival	636 days	792 days	592 days
Odds Ratio for Response	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*
Relative Risk of Progression	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 curves for progression for the aminoglutethimide study is shown in Figure 5.

Figure 5 Kaplan-Meier Estimates of Time to Progression (Aminoglutethimide Study)



16 HOW SUPPLIED/STORAGE AND HANDLING

Packaged in HDPE bottles with a safety screw cap.

2.5 milligram tablets

Bottles of 30 tablets……NDC 0078-0249-15

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

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

Pregnancy: Femara is contraindicated in women of premenopausal endocrine status. The physician needs to discuss the necessity of adequate contraception with women who have the potential to become pregnant including women who are perimenopausal or who recently became postmenopausal, until their postmenopausal status is fully established.

Fatigue and Dizziness: Since fatigue and dizziness have been observed with the use of Femara and somnolence was uncommonly reported, caution is advised when driving or using machinery.

Bone Effects: Consideration should be given to monitoring bone mineral density.

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