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

----------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: 1/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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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.

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 with 73% of the patients having completed adjuvant therapy. 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. In the final updated analysis, conducted at a median follow-up of 62 months, the median treatment duration was 60 months. Seventy-one percent 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 the clinical benefit to premenopausal women with breast cancer has not been demonstrated. Femara is contraindicated in women who are or may become pregnant. If Femara 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. Results of a substudy to evaluate safety in the adjuvant setting comparing the effect on lumbar spine (L2-L4) bone mineral density (BMD) of adjuvant treatment with letrozole to that with tamoxifen showed at 24 months a median decrease in lumbar spine BMD of 4.1% in the letrozole arm compared to a median increase of 0.3% in the tamoxifen arm (difference = 4.4%) ($P<0.0001$) *[see Adverse reactions (6.1)]*. Updated results from the BMD substudy in the extended adjuvant setting 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 significantly different *[see Adverse Reactions (6.2)]*.

In the adjuvant trial the incidence of bone fractures at any time after randomization was 13.8% for letrozole and 10.5% for tamoxifen. The incidence of osteoporosis was 5.1% for letrozole and 2.7% for tamoxifen *[see Adverse Reactions (6.1)]*. In the extended adjuvant trial the incidence of bone fractures at any time after randomization was 13.3% for letrozole and 7.8% for placebo. The incidence of new osteoporosis was 14.5% for letrozole and 7.8% for placebo *[see Adverse Reactions (6.3)]*.

5.2 Cholesterol

Consideration should be given to monitoring serum cholesterol. In the adjuvant trial hypercholesterolemia was reported in 52.3% of letrozole patients and 28.6% of tamoxifen patients. CTC grade 3-4 hypercholesterolemia was reported in 0.4% of letrozole patients and 0.1% of tamoxifen patients. Also in the adjuvant setting, an increase of ≥1.5 X ULN in total cholesterol (generally non-fasting) was observed in patients on monotherapy who had baseline total serum cholesterol within the normal range (i.e., <=1.5 X ULN) in 151/1843 (8.2%) on letrozole vs 57/1840 (3.2%). Lipid lowering medications were required for 25% of patients on letrozole and 16% on tamoxifen *[see Adverse Reactions (6.1)]*.

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)]*

Because clinical trials are 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 treatment duration of adjuvant treatment was 60 months and the median duration of follow-up for safety was 73 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 (approximately 75% of patients reporting 1 or more AE) were Grade 1 or Grade 2 applying the Common Toxicity Criteria Version 2.0/ Common Terminology Criteria for Adverse Events, version 3.0. Table 1 describes adverse reactions (Grades 1-4) irrespective of relationship to study treatment in the adjuvant trial for the monotherapy arms analysis (safety population).

Table 1: Patients with Adverse Reactions (CTC Grades 1-4, Irrespective of Relationship to Study Drug) in the Adjuvant Study – Monotherapy Arms Analysis (Median Follow-up 73 Months; Median Treatment 60 Months)

	Grades 1-4				Grades 3-4			
Adverse Reaction	**Femara N=2448 n (%)**		**tamoxifen N=2447 n (%)**		**Femara N=2448 n (%)**		**tamoxifen N=2447 n (%)**	
Pts with any adverse event	2310	(94.4)	2214	(90.5)	635	(25.9)	604	(24.7)
Hypercholesterolemia	1280	(52.3)	700	(28.6)	11	(0.4)	6	(0.2)
Hot Flashes/Flushes	821	(33.5)	929	(38.0)	0	-	0	-
Arthralgia/Arthritis	618	(25.2)	501	(20.4)	85	(3.5)	50	(2.0)
Night Sweats	357	(14.6)	426	(17.4)	0	-	0	-
Bone Fractures[2]	338	(13.8)	257	(10.5)	-	-	-	-
Weight Increase	317	(12.9)	378	(15.4)	27	(1.1)	39	(1.6)
Nausea	283	(11.6)	277	(11.3)	6	(0.2)	9	(0.4)
Bone Fractures[1]	247	(10.1)	174	(7.1)	-	-	-	-
Fatigue (Lethargy, Malaise, Asthenia)	235	(9.6)	250	(10.2)	6	(0.2)	7	(0.3)
Myalgia	217	(8.9)	212	(8.7)	18	(0.7)	14	(0.6)
Edema	164	(6.7)	160	(6.5)	3	(0.1)	1	(<0.1)
Weight Decrease	140	(5.7)	129	(5.3)	8	(0.3)	5	(0.2)
Vaginal Bleeding	128	(5.2)	320	(13.1)	1	(<0.1)	8	(0.3)
Back Pain	125	(5.1)	136	(5.6)	7	(0.3)	11	(0.4)
Osteoporosis NOS	124	(5.1)	66	(2.7)	10	(0.4)	5	(0.2)
Bone pain	123	(5.0)	109	(4.5)	6	(0.2)	4	(0.2)
Depression	119	(4.9)	114	(4.7)	16	(0.7)	14	(0.6)
Vaginal Irritation	111	(4.5)	77	(3.1)	2	(<0.1)	2	(<0.1)
Headache	105	(4.3)	94	(3.8)	9	(0.4)	5	(0.2)
Pain in extremity	103	(4.2)	79	(3.2)	6	(0.2)	4	(0.2)
Osteopenia	87	(3.6)	74	(3.0)	0	-	2	(<0.1)
Dizziness/Light-Headedness	84	(3.4)	84	(3.4)	1	(<0.1)	6	(0.2)
Alopecia	83	(3.4)	84	(3.4)	0	-	0	-
Vomiting	80	(3.3)	80	(3.3)	3	(0.1)	5	(0.2)
Cataract	49	(2.0)	54	(2.2)	16	(0.7)	17	(0.7)
Constipation	49	(2.0)	71	(2.9)	3	(0.1)	1	(<0.1)
Breast pain	37	(1.5)	43	(1.8)	1	(<0.1)	0	-
Anorexia	20	(0.8)	20	(0.8)	1	(<0.1)	1	(<0.1)

[3]								
Endometrial Proliferation Disorders	10	(0.3)	71	(1.8)	0	-	14	(0.6)
Endometrial Hyperplasia/ Cancer[1,3]	6/1909	(0.3)	57/1943	(2.9)	-	-	-	-
Other Endometrial Disorders	2	(<0.1)	3	(0.1)	0	-	0	-
Myocardial Infarction[1]	24	(1.0)	12	(0.5)	-	-	-	-
Myocardial Infarction[2]	37	(1.5)	25	(1.0)	-	-	-	-
Myocardial Ischemia	6	(0.2)	9	(0.4)	-	-	-	-
Cerebrovascular Accident[1]	52	(2.1)	46	(1.9)	-	-	-	-
Cerebrovascular Accident[2]	70	(2.9)	63	(2.6)	-	-	-	-
Angina[1]	26	(1.1)	24	(1.0)	-	-	-	-
Angina[2]	32	(1.3)	31	(1.3)	-	-	-	-
Thromboembolic Event[1]	51	(2.1)	89	(3.6)	-	-	-	-
Thromboembolic Event[2]	71	(2.9)	111	(4.5)	-	-	-	-
Other Cardiovascular[1]	260	(10.6)	256	(10.5)	-	-	-	-
Other Cardiovascular[2]	312	(12.7)	337	(13.8)	-	-	-	-
Second Malignancies[1]	53	(2.2)	78	(3.2)	-	-	-	-
Second Malignancies[2]	102	(4.2)	119	(4.9)	-	-	-	-

[1] During study treatment, based on Safety Monotherapy population

[2] Any time after randomization, including post treatment follow-up

[3] Excluding women who had undergone hysterectomy before study entry

Note: Cardiovascular (including cerebrovascular and thromboembolic), skeletal and urogenital/endometrial events and second malignancies were collected life-long. All of these events were assumed to be of CTC Grade 3 to 5 and were not individually graded.

When considering all grades during study treatment, a higher incidence of events was seen for Femara regarding fractures (10.1% vs 7.1%), myocardial infarctions (1.0% vs 0.5%), and arthralgia (25.2% vs 20.4%) (Femara vs tamoxifen respectively). A higher incidence was seen for tamoxifen regarding thromboembolic events (2.1% vs 3.6%), endometrial hyperplasia/cancer (0.3% vs 2.9%), and endometrial proliferation disorders (0.3% vs 1.8%) (Femara vs tamoxifen respectively).

At a median follow up of 73 months, a higher incidence of events was seen for Femara (13.8%) than for tamoxifen (10.5%) regarding fractures. A higher incidence was seen for tamoxifen compared to Femara regarding thromboembolic events (4.5% vs 2.9%), and endometrial hyperplasia or cancer (2.9% vs 0.4%) (tamoxifen vs Femara, respectively).

Bone Study: Results of a phase 3 safety trial in 262 postmenopausal women with resected receptor positive early breast cancer in the adjuvant setting comparing the effect on lumbar spine (L2-L4) bone mineral density (BMD) of adjuvant treatment with letrozole to that with tamoxifen showed at 24 months a median decrease in lumbar spine BMD of 4.1% in the letrozole arm compared to a median increase of 0.3% in the tamoxifen arm (difference = 4.4%) (P<0.0001). No patients with a normal BMD at baseline became osteoporotic over the 2 years and only 1 patient with osteopenia at baseline (T score of -1.9) developed osteoporosis during the treatment period (assessment by central review). The results for total hip BMD were similar, although the differences between the two treatments were less pronounced. During the 2 year period, fractures were reported by 4 of 103 patients (4%) in the letrozole arm, and 6 of 97 patients (6%) in the tamoxifen arm.

Lipid Study: In a phase 3 safety trial in 262 postmenopausal women with resected receptor positive early breast cancer at 24 months comparing the effects on lipid profiles of adjuvant letrozole to tamoxifen, 12% of patients on letrozole had at least one total cholesterol value of a higher CTCAE grade than at baseline compared with 4% of patients on tamoxifen.

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

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