DOCUMENT INFORMATION PAGE

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END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-876/S-008

Novartis Pharmaceuticals Corporation
One Health Plaza, Building 105/2W200
Hanover, New Jersey 07936-1080

Attention: Arlene Wolny, Associate Director
Drug Regulatory Affairs

Dear Ms. Wolny:

Please refer to your supplemental new drug application dated March 15, 2002, received March 18, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Femara® (letrozole) tablets, 2.5 mg.

We acknowledge receipt of your submissions dated November 15, 2002 and January 2, 2003.

This supplemental new drug application provides for updating the safety and efficacy data for Femara® for first-line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer and includes revisions to the Clinical Studies, Precautions, and Adverse Reactions sections of the labeling.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-876/S-008." Approval of this submission by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/ the Division of Oncology Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane

Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Ann Staten, Regulatory Project Manager, at (301) 594-0490.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

NOVARTIS

T2003 - XX
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Femara®
(letrozole tablets)

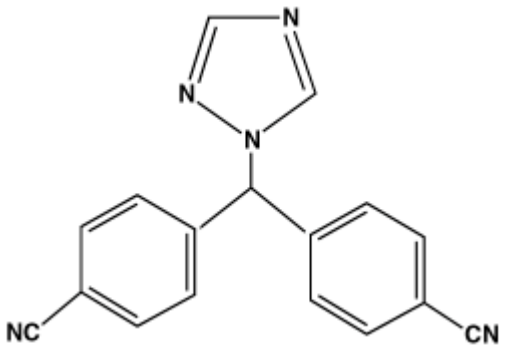
2.5 mg Tablets

Rx only

Prescribing Information

DESCRIPTION

Femara® (letrozole 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 184ºC-185ºC.

Femara® (letrozole tablets) 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.

CLINICAL PHARMACOLOGY

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.

Pharmacokinetics

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.

Special Populations

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 Insufficiency

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® (letrozole tablets) 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 concentration.

Hepatic Insufficiency

In a study of subjects with varying degrees of 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. Patients with severe hepatic impairment (Child-Pugh classification C) have not been studied (see DOSAGE AND ADMINISTRATION, Hepatic Impairment).

Drug/Drug Interactions

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

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

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.

Clinical Studies

First-Line Breast Cancer

A randomized, double-blinded, multinational trial compared Femara 2.5 mg with tamoxifen 20 mg in 916 postmenopausal patients with locally advanced (Stage IIIB or locoregional 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 1.

Table 1: Selected Study Population Demographics

Baseline Status	**Femara® N = 458**	**tamoxifen 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 2).

Table 2 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 2: Results

	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 1 shows the Kaplan-Meier curves for TTP.

Table 3 shows results in the subgroup of women who had received prior antiestrogen adjuvant therapy, Table 4, results by disease site and Table 5, the results by receptor status.

Figure 1
KAPLAN-MEIER ESTIMATES OF TIME TO PROGRESSION
(TAMOXIFEN STUDY)

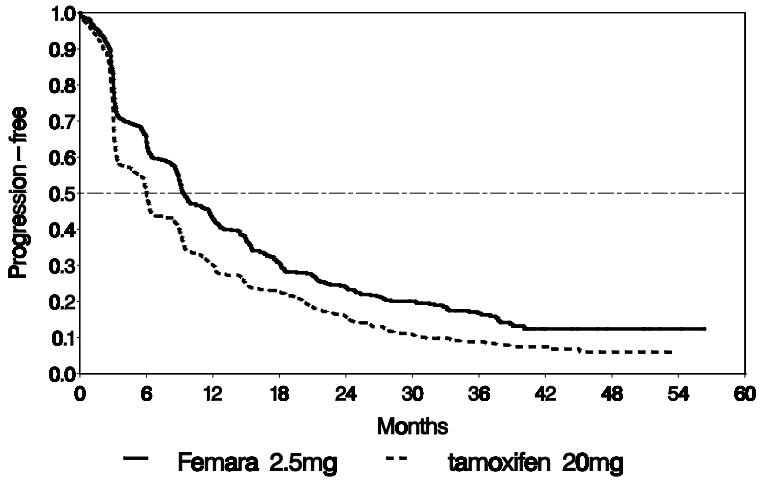


Table 3:

Efficacy in patients who received prior antiestrogen therapy

Variable	Femara 2.5 mg	tamoxifen 20 mg
	n=84	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)	

Variable	Femara 2.5 mg	tamoxifen 20 mg
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 letrozole; hazard ratio greater than 1 or odds ratio less than 1 favors tamoxifen.

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Table 4: 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 5:

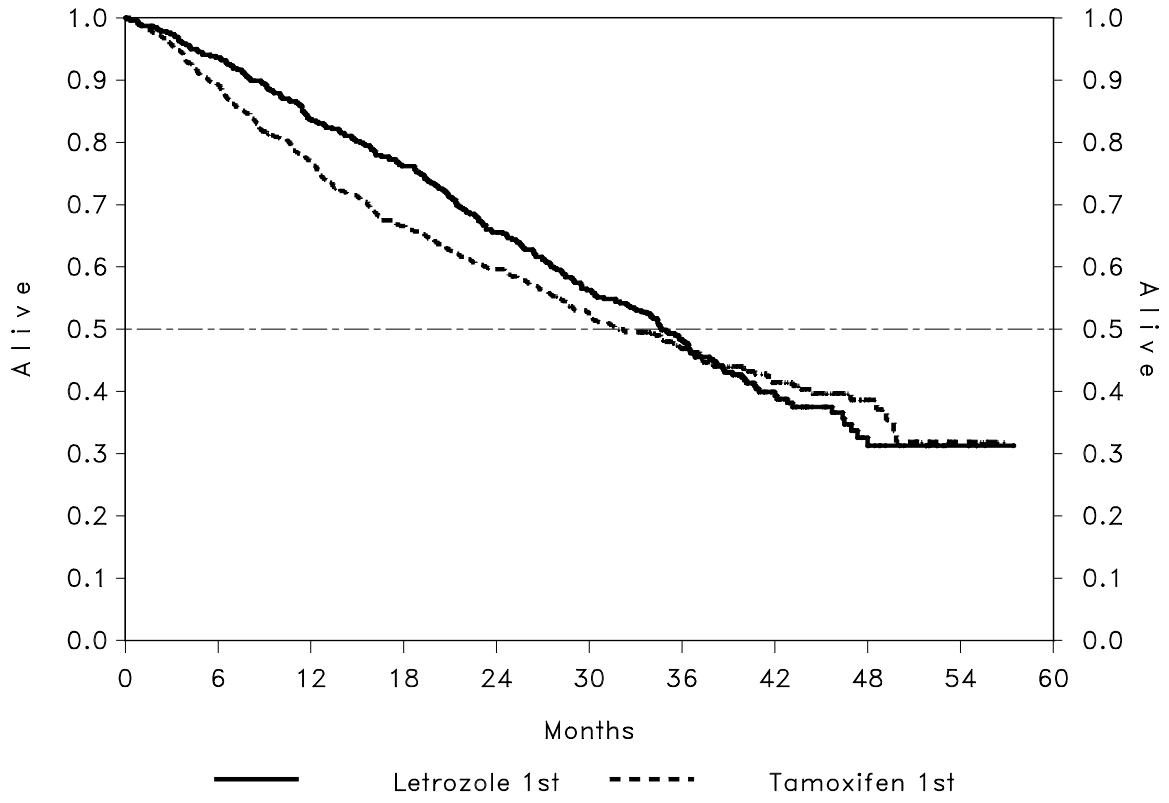
Efficacy by receptor status

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

Figure 2 shows the Kaplan-Meier curves for survival

Figure 2 Survival by randomized treatment arm



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

The median overall survival was 35 months for the letrozole 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 cross-over was 17 months (Femara to tamoxifen) and 13 months (tamoxifen to Femara). In patients who did not crossover to the opposite treatment arm, median survival was 35 months with Femara (n=219, 95% CI 29 to 43 months) vs. 20 months with tamoxifen (n=229, 95% CI 16 to 26 months).

Second-Line 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 6.

Table 6: 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%
Visceral	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 7 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 7: Megestrol Acetate Study Results

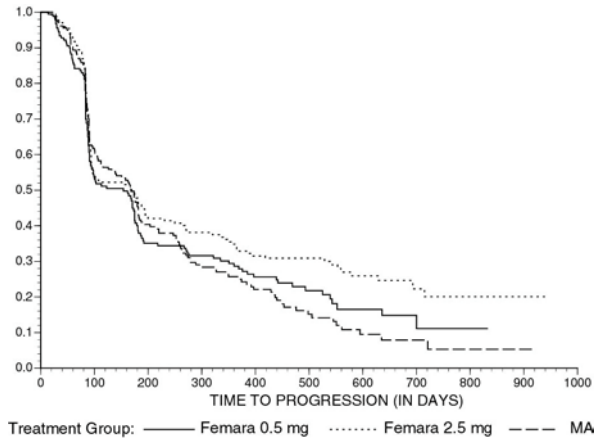
	Femara® 0.5 mg N = 188	Femara® 2.5 mg N = 174	megestrol acetate N = 190
Objective Response (CR + PR)	22 (11.7%)	41 (23.6%)	31 (16.3%)

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 Curve for progression for the megestrol acetate study is shown in Figure 3.

Figure 3
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 nine months, are shown in Table 8. (Unadjusted analyses are used.)

Table 8: Aminoglutethimide Study Results

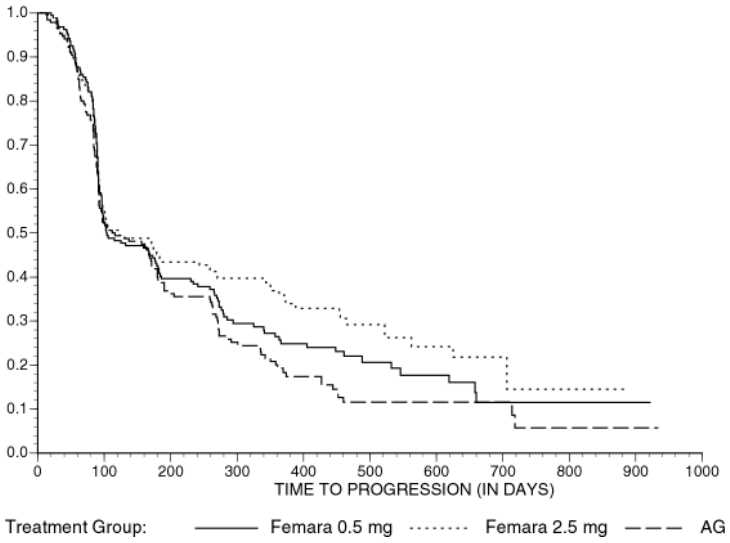
	Femara® 0.5 N = 193	**Femara® 2.5 N = 185**	**aminoglutethimide N = 179**
Objective Response (CR + PR)	34 (17.6%)	34 (18.4%)	22 (12.3%)
Median Duration of Response	619 days	706 days	450 days
Median Time to Progression	103 days	123 days	112 days
Median Survival	636 days	792 days	592 days
Odds Ratio for Response	Femara 2.5 : Femara 0.5 =1.05		Femara 2.5: aminoglutethimide=1.61

	(95% CI: 0.62, 1.79); p=0.85*	(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 Curve for progression for the aminoglutethimide study is shown in Figure 4.

Figure 4
KAPLAN-MEIER ESTIMATES OF TIME TO PROGRESSION
(AMINOGLUTETHIMIDE STUDY)



INDICATIONS AND USAGE

Femara® (letrozole tablets) is indicated for first-line treatment of postmenopausal women with hormone receptor positive or hormone receptor 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.

CONTRAINDICATIONS

Femara® (letrozole tablets) is contraindicated in patients with known hypersensitivity to Femara or any of its excipients.

WARNINGS

Pregnancy

Letrozole may cause fetal harm when administered to pregnant women. Studies in rats at 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 hindlegs.

There are no studies in pregnant women. Femara® (letrozole tablets) is indicated for post-menopausal women. If there is exposure to letrozole during pregnancy, the patient should be apprised of the potential hazard to the fetus and potential risk for loss of the pregnancy.

PRECAUTIONS

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.

Laboratory Tests

No dose-related effect of Femara® (letrozole tablets) 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.

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

Drug Interactions

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

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

Drug/Laboratory Test-Interactions

None observed.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A conventional carcinogenesis study in mice at doses of 0.6 to 60 mg/kg/day (about one 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.

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).

Pregnancy

Pregnancy Category D (see WARNINGS).

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

The median age of patients in the trial that compared Femara 2.5 mg daily to tamoxifen 20 mg daily as first-line therapy was 65 years. About 1/3 of the patients were ≥70 years old. Femara time to tumor progression and tumor response rate were better in patients ≥70 than in patients <70 years of age.

The mean age of patients in the two second-line randomized trials, that compared Femara (0.5 mg and 2.5 mg) to megestrol acetate and to aminoglutethimide, was 64 years. Thirty percent of patients were ≥70 years old. The proportion of patients responding to each dose of Femara was similar for women ≥70 years old and <70 years old.

ADVERSE REACTIONS

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

First-Line Breast Cancer

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

Adverse events, 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 9.

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

Adverse Experience	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 not otherwise specified	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 not otherwise specified	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 not otherwise specified	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 experiences 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.

Second-Line Breast Cancer

Femara was generally well tolerated in two controlled clinical trials.

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

Comparisons of the incidence of adverse events revealed no significant differences between the high and low dose Femara groups in either study. Most of the adverse events 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 events, 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 10.

Table 10: Percentage (%) of Patients with Adverse Events

Adverse Experience	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, psoriaform rash, vesicular rash

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

OVERDOSAGE

Isolated cases of Femara® (letrozole tablets) overdose have been reported. In these instances, the highest single dose ingested was 62.5 mg or 25 tablets. While no serious adverse events 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 2000 mg/kg (about 4000 to 8000 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.

DOSAGE AND ADMINISTRATION

Adult and Elderly Patients

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

Renal Impairment

(See CLINICAL PHARMACOLOGY.) No dosage adjustment is required for patients with renal impairment if creatinine clearance is ≥10 mL/min.

Hepatic Impairment

(See CLINICAL PHARMACOLOGY.) Although letrozole blood concentrations were modestly increased in subjects with moderate hepatic impairment due to cirrhosis, no dosage adjustment is recommended for patients with mild-to-moderate hepatic impairment. Patients with severe impairment of liver function have not been studied. Because letrozole is eliminated almost exclusively by hepatic metabolism, patients with severe impairment of liver function should be dosed with caution.

HOW SUPPLIED

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).

Packaged in HDPE bottles with a safety screw cap.

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

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

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NOVARTIS

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Grant Williams
1/17/03 12:30:41 PM
Signed for Dr. Pazdur