NOVARTIS

Femara®

(letrozole tablets)

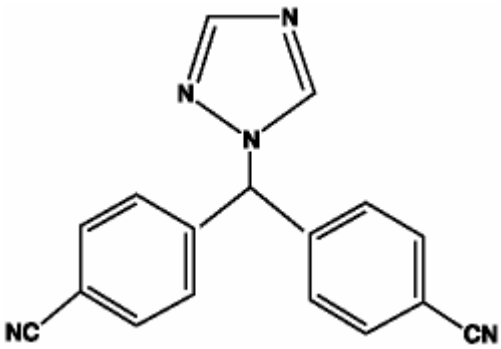
2.5 mg Tablets

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 184°C-185°C.

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 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 pharmacokinetics 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, 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. In *in-vitro* experiments, letrozole showed no significant inhibition in the metabolism of diazepam. Similarly, no significant inhibition of letrozole metabolism by diazepam was observed.

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 pivotal trials indicates that the therapeutic effect of Femara therapy is not impaired if Femara is administered immediately after tamoxifen.

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

Adjuvant Treatment of Early Breast Cancer in Postmenopausal Women

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, 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 2 reflect 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 1.

Table 1: 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 2: 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)	0.0005
Node Negative			0.92 (0.70, 1.22)	0.572
Prior Adjuvant Chemotherapy			0.70 (0.53, 0.93)	0.013
No Chemotherapy			0.83 (0.69, 1.00)	0.046
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)	0.0005
Node Negative			0.90 (0.60, 1.34)	0.597
Prior Adjuvant Chemotherapy			0.69 (0.50, 0.95)	0.024
No Chemotherapy			0.75; (0.60, 0.95)	0.018
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)	0.113
Node Negative			0.88 (0.59, 1.30)	0.507
Prior Adjuvant Chemotherapy			0.76 (0.51, 1.14)	0.185

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