PRODUCT MONOGRAPH

PrFEMARA®

(letrozole tablets)

2.5 mg

Non-steroidal aromatase inhibitor;
inhibitor of estrogen biosynthesis;
anti-tumour agent

Novartis Pharmaceuticals Canada Inc.
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(letrozole tablets)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Pharmaceutical Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablets, 2.5 mg	Lactose *For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

INDICATIONS AND CLINICAL USE

FEMARA® (letrozole) is indicated for:

- the adjuvant treatment of postmenopausal women with hormone receptor-positive invasive early breast cancer.

  Clinical effectiveness is based on superior Disease-Free Survival (DFS) compared to tamoxifen. Overall survival was not significantly different between the two treatments (see **CLINICAL TRIALS** section).

- The extended adjuvant treatment of hormone receptor-positive invasive early breast cancer in postmenopausal women who have received approximately 5 years of prior standard adjuvant tamoxifen therapy.

  Clinical effectiveness is based on superior Disease-Free Survival (DFS) compared to placebo in the overall study population, at a median follow-up of 28 months. However, overall survival was not significantly different between the two treatments for the overall population and an increase in deaths was seen in node-negative patients in the FEMARA arm versus the placebo arm (see **WARNINGS AND PRECAUTIONS and CLINICAL TRIALS** sections).

- First-line therapy in postmenopausal women with advanced breast cancer.

- The hormonal treatment of advanced/metastatic breast cancer after relapse or disease progression, in women with natural or artificially-induced postmenopausal endocrine status, who have previously been treated with anti-estrogens.

FEMARA is not indicated in hormone-receptor negative disease

Men

Use of FEMARA in men with breast cancer has not been studied (See WARNINGS AND PRECAUTIONS section, Sexual Function/Reproduction).

CONTRAINDICATIONS

- Patients who are hypersensitive to letrozole, other aromatase inhibitors, or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.
- Premenopausal women (see **WARNINGS AND PRECAUTIONS** section).
- Pregnant women (see **WARNINGS AND PRECAUTIONS** section).
- Breast-feeding women (see **WARNINGS AND PRECAUTIONS** section).
- In the absence of clinical experience with the use of FEMARA in children or adolescents (under 18 years of age), FEMARA should not be used in these patients.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

FEMARA (letrozole) should be prescribed and managed by a qualified physician who is experienced in the use of anti-cancer agents.

FEMARA increases the risk of osteoporosis and bone fractures.

General

No studies on the effects of FEMARA on the ability to drive and use machines have been performed. However, since fatigue, dizziness, and uncommonly somnolence have been observed with the use of FEMARA, caution is advised when driving or operating machinery while such symptoms persist.

Co-administration of FEMARA with tamoxifen, other anti-estrogens or estrogen-containing therapies should be avoided as these substances may diminish the efficacy of letrozole. (see **INTERACTIONS** section).

The benefit risk assessment should be carefully considered prior to prescribing FEMARA as extended adjuvant treatment for early breast cancer patients with low risk of recurrence. The risk of death in the node-negative subgroup was increased by ~35% in patients treated with FEMARA compared to patients receiving placebo at median follow-up of 28 months (HR: 1.36; 95% CI: 0.68, 1.81) and 62 months (HR 1.34; 95% CI: 0.99, 1.81) in the MA-17 study (see **CLINICAL TRIALS** section).

Cardiovascular Disease

The use of aromatase inhibitors, including FEMARA, may increase the risk of cardiovascular events (see **ADVERSE REACTIONS** section).

The overall incidence of cardiovascular events in the BIG 1-98 study at a median treatment duration of 25 months for FEMARA and tamoxifen was 10.1% vs. 11.4%, respectively. A significantly higher incidence of events was seen for FEMARA vs. tamoxifen in cardiac failure (0.8% vs. 0.3%), and a significantly lower incidence in thromboembolic events (1.2% vs. 3.0%). Numerically (but not significantly) more cases of myocardial infarction were seen with FEMARA (20, 0.5%) than with tamoxifen (15, 0.4%), as well as hypertension (151, 3.8% vs. 137, 3.4%, respectively), ischemic cardiovascular events (60, 1.5% vs. 55, 1.4%, respectively), and cerebrovascular events (55, 1.4% vs. 50, 1.3%, respectively); and, reported any time after randomization (irrespective of treatment and irrespective of a cancer event) at a median follow up of 30 months, fatal cardiac events (18, 0.4% vs. 7, 0.2% respectively) and fatal stroke (7, 0.2% vs. 5, 0.2% respectively).

The overall incidence of cardiovascular events (including cerebrovascular and thromboembolic events) in the BIG 1-98 study for FEMARA and tamoxifen at a median treatment duration of 60 months and a median follow-up of 96 months was 15.3 % vs. 16.3%, respectively (a non-significant difference). During treatment, or within 30 days of stopping treatment, a significantly higher risk of myocardial infarction was observed for FEMARA (1.0%) than for tamoxifen (0.5%) (Risk Ratio, RR: 2.00; 95% CI 1.00, 3.99) while a significantly lower risk of thromboembolic events was seen for FEMARA (2.1%) than for tamoxifen (3.6%) (RR: 0.57; 95% CI 0.41, 0.80). Numerically (but not significantly) more cases of cardiac failure were seen with FEMARA (1.1%) than with tamoxifen. (0.6%) (RR 1.80; 95% CI 0.96, 3.37).

In the extended adjuvant setting, in the updated analysis of MA-17, the overall incidence of cardiovascular events (including cerebrovascular and thromboembolic events) during treatment or within 30 days of stopping treatment (median duration of treatment of 60 months) was significantly higher for FEMARA (9.8%) than for placebo (7.0%) (RR: 1.39; 95% CI 1.16, 1.67). There was a higher risk of stroke/transient ischemic attack with FEMARA (1.5%) than with placebo (0.8%) (RR 1.86; 95% CI 1.10, 3.16) and of thromboembolic events with

FEMARA (0.9%) than with placebo (0.3%) (RR 2.57; 95% CI 1.19, 5.53) (see **ADVERSE REACTIONS** section).

At a median treatment period of 60 months, the number of deaths during treatment or within 30 days of stopping treatment was slightly higher in the placebo arm [82/2577 (3.2%)] than in the FEMARA arm [77/2567 (3.0%)], but the difference was not statistically significant. Of the 19 deaths attributed to a cardiovascular cause in the placebo arm, 12 occurred in the group of 1026 patients who did not switch to FEMARA after study unblinding, and 7 occurred in the group of 1551 patients who switched to FEMARA. A total of 7 patients died from a stroke – 6 in the FEMARA arm and 1 after switching from placebo to FEMARA after study unblinding.

Endocrine and Metabolism

Hyperlipidemia: The use of aromatase inhibitors, including FEMARA, may increase lipid levels. In the adjuvant therapy trial (BIG 1-98), at a median treatment duration of 60 months, hypercholesterolemia was reported in 52.3% of patients treated with FEMARA compared to 28.6% of patients treated with tamoxifen. In a smaller study (D2407) comparing 2 years of adjuvant treatment with FEMARA or tamoxifen, significant differences were observed between treatments at all time-points in total cholesterol, LDL cholesterol and the HDL: LDL ratio in favour of tamoxifen. Clinically relevant changes in total cholesterol at 2 years occurred significantly more often for patients treated with FEMARA (17%) than with tamoxifen (5%). Monitoring of serum cholesterol is advised for patients treated with FEMARA. (see also ADVERSE REACTIONS, ACTION AND CLINICAL PHARMACOLOGY, CLINICAL TRIALS and DETAILED PHARMACOLOGY sections).

Musculoskeletal

Bone Mineral Density: The use of estrogen lowering agents, including FEMARA, may cause a reduction in bone mineral density (BMD) with a possible consequent increased risk of osteoporosis and fracture.

During study treatment or within 30 days of stopping treatment in study BIG 1-98 (median treatment duration of 60 months and a median follow-up of 96 months), there was a significantly higher incidence of osteoporosis in patients treated with FEMARA (5.1%) than with tamoxifen (2.7%). Similarly, significantly more patients receiving FEMARA experienced bone fractures (10.2%) than those receiving tamoxifen (7.2%). During treatment or within 30 days of stopping treatment (median duration of treatment of 60 months) in study MA-17, there was a significantly higher incidence of osteoporosis in patients treated with FEMARA (12.2%) than with placebo (6.4%). Similarly, significantly more patients receiving FEMARA experienced bone fractures (10.4%) than those receiving placebo (5.8%). Therefore, monitoring of overall bone health is recommended during treatment with FEMARA. Women should have their osteoporosis risk assessed and managed according to local clinical practice and guidelines (see also **Special Populations – Geriatrics, ADVERSE REACTIONS, ACTION AND CLINICAL PHARMACOLOGY, CLINICAL TRIALS and DETAILED PHARMACOLOGY** sections).

Arthralgia/arthritis: In the adjuvant setting, a significantly increased risk of arthralgia/arthritis was reported with FEMARA (25.4%) compared to tamoxifen (20.6%) at a median treatment duration of 60 months. In a smaller study (D2407) which reported two years adjuvant treatment, arthralgia/arthritis was reported in 26% of patients who received FEMARA compared with 15% who received tamoxifen (significant difference).

In the extended adjuvant setting, in the original analysis of the double-blind study, significantly more patients treated with FEMARA (28%) than with placebo (22%) experienced arthralgia/arthritis (median duration of treatment 24 months).

Myalgia: In the adjuvant setting, the risk of myalgia was not significantly higher for FEMARA (9.0%) than for tamoxifen (8.7%) (study BIG 1-98). In a smaller study (D2407) after two years of adjuvant therapy, myalgia was reported for 3.8% of patients with FEMARA and for 0.8% of patients with tamoxifen (difference not statistically significant).

In the extended adjuvant setting, myalgia was reported significantly more often for FEMARA, (9.5%) than for placebo (6.7%) (median duration of treatment 24 months).

Sexual Function/Reproduction

Reproductive Toxicology: Letrozole was evaluated for maternal toxicity as well as embryotoxic, fetotoxic and teratogenic potential in female rats and rabbits. Oral administration of letrozole to pregnant Sprague-Dawley rats resulted in teratogenicity and maternal toxicity at 0.03 mg/kg (about 1/10 the daily maximum recommended human dose (MRHD)), and embryotoxicity and fetotoxicity at doses ≥0.003 mg/kg (about 1/100 the daily MRHD). Teratogenic effects included fetal domed head and cervical/centrum vertebral fusion. Embryotoxic and fetotoxic effects included 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. In New Zealand White rabbits, letrozole was embryotoxic at doses ≥ 0.002 mg/kg, and fetotoxic when administered at 0.02 mg/kg (about 1/100,000 and 1/10,000 the daily MRHD). Fetal anomalies included incomplete ossification of the skull, sternebrae, and forelegs and hind legs. It is not known whether these effects are an indirect consequence of the pharmacological activity of FEMARA (inhibition of estrogen biosynthesis) or a direct drug effect.

Fertility: The pharmacological action of letrozole is to reduce estrogen production by aromatase inhibition. In premenopausal women, the inhibition of estrogen synthesis leads to feedback increases in gonadotropin (LH, FSH) levels, stimulation of follicular growth, and ovulation induction (see **Monitoring and Laboratory Tests** section). In premenopausal women, these feedback mechanisms increase the risk of inducing ovarian hyperstimulation syndrome. In addition, spontaneous abortions and congenital anomalies have been reported in infants born to women exposed to FEMARA while pregnant. Letrozole is contraindicated in premenopausal women (see **CONTRAINDICATIONS** section).

Based on animal studies, Femara may impair fertility in males of reproductive potential (See Reproductive and Developmental Toxicity)

Special Populations

Hepatic Impairment: In a single dose trial with 2.5 mg letrozole in volunteers with impairment of hepatic function, mean AUC values of the volunteers with moderate hepatic impairment (Child-Pugh score B) was 37% higher than in normal volunteers, but still within the range seen in volunteers with normal hepatic function. In a study comparing the pharmacokinetics of letrozole after a single oral dose of 2.5 mg in eight volunteers with liver cirrhosis and severe non-metastatic hepatic impairment (Child-Pugh score C) to those in healthy volunteers (N=8), AUC and $t_{½}$ increased by 95% and 187%, respectively. Breast cancer patients with severe hepatic impairment are thus expected to be exposed to higher levels of letrozole than patients without severe hepatic dysfunction. Long term effects of this increased exposure have not been studied.

These results indicate that no dosage adjustment is necessary for breast cancer patients with mild to moderate hepatic dysfunction. However, since letrozole elimination depends mainly on intrinsic metabolic clearance, caution is recommended. Insufficient data are available to recommend a dose adjustment in breast cancer patients with severe non-metastatic hepatic impairment. Therefore, such patients should be kept under close supervision for adverse events.

Renal Impairment: Pharmacokinetics of a single 2.5 mg letrozole dose were unchanged in a study in postmenopausal women with varying degrees of renal function (24-hour creatinine clearance = 9 - 116 mL/min). In a study in 364 patients with advanced breast cancer there was no significant association between letrozole plasma levels and calculated CL_{cr} (range 22.9 - 211.9 mL/min).

No dosage adjustment is required in patients with $CL_{cr} \geq 10$ mL/min. No data are available for patients with $CL_{cr} \leq 9$ mL/min. The potential risks and benefits to such patients should be considered carefully before prescribing letrozole.

Pregnant Women: Letrozole must not be given to pregnant women (see **CONTRAINDICATIONS** section). Isolated cases of birth defects (labial fusion, ambiguous genitalia) have been reported in infants born to women exposed to FEMARA during pregnancy (see also **Sexual Function/Reproduction - Reproductive Toxicology** section).

Women of Child-Bearing Potential: There are no clinical trials conducted in pregnant women with FEMARA. However, there are post-marketing reports of spontaneous abortions and congenital anomalies in infants of mothers who took FEMARA during pregnancy. Letrozole should not be given to women with premenopausal endocrine status (see **CONTRAINDICATIONS** section). Women who are not premenopausal but have the potential to become pregnant, including women who are perimenopausal or who recently became postmenopausal, should use appropriate contraception (methods that result in less than 1 %

pregnancy rates) while being treated with FEMARA and for *20 days* after stopping treatment with FEMARA (see also **Sexual Function/Reproduction - Reproductive Toxicology** section).

Nursing Women: Letrozole must not be administered to nursing mothers (see **CONTRAINDICATIONS** section). It is not known if Letrozole is excreted in human milk. There are no data on the effects of FEMARA on the breastfed child or the effects of FEMARA on milk production, however, exposure of FEMARA in lactating rats led to impaired fertility of male offspring (See Reproductive and Developmental Toxicity).

Women of Unclear Menopausal status: Women treated with letrozole whose menopausal status has not been confirmed are at an increased risk of becoming pregnant and experiencing spontaneous abortions or congenital anomalies in their infants (see also **Sexual Function/Reproduction - Reproductive Toxicology** section). In patients whose menopausal status is unclear or who become amenorrheic after chemotherapy, luteinising hormone (LH), follicle-stimulating hormone (FSH) and/or estradiol levels should be measured before initiating treatment with FEMARA and regularly during the first 6 months of treatment. Appropriate contraception should be used to avoid pregnancy. Only women of confirmed postmenopausal endocrine status should receive FEMARA.

Geriatrics (≥ 65 years of age): There have been no age-related effects observed on the pharmacokinetics of letrozole. No major difference in general safety was observed in patients aged < 65 years versus ≥ 65 years; however, patients ≥ 65 years experienced more bone fractures and more osteoporosis, irrespective of treatment.

In the adjuvant setting, more than 8000 postmenopausal women were enrolled in the clinical study (see **CLINICAL TRIALS** section). In total, 36% of patients were aged 65 years or older at enrolment, while 12% were 75 or older. Although more adverse events were generally reported in elderly patients irrespective of study treatment allocation, the differences between the two treatment groups were similar to those of younger patients.

In the extended adjuvant study, more than 5000 postmenopausal women were enrolled in the study; 41% of the patients were aged 65 years or older at enrolment, while 12% were 75 or older.

In the extended adjuvant study, after a median follow-up of 28 months, fracture rates recorded any time after randomization in patients 65 years and older at study enrolment were 7.1% (77/1090) in the FEMARA arm compared to 7.5 % (77/1033) in the placebo arm; the difference is not statistically significant (P= 0.74). These results were obtained prior to study unblinding.

In the extended adjuvant study, after a median treatment of 60 months for FEMARA, fracture rates reported during treatment or within 30 days of stopping treatment in patients aged 65 years or older at enrollment were 11.4% (124/1091) for FEMARA compared to 7.7% (79/1032) for placebo until switch, and 11.2% (59/528) for patients switching from placebo to FEMARA. After a median follow-up of 62 months for FEMARA, fracture rates reported any time after randomization in patients aged 65 years or older at enrollment were 15.7% (171/1091) for

FEMARA compared to 11.5% (119/1032) for placebo, and 11.9% (63/528) for FEMARA after switch.

Monitoring and Laboratory Tests

Plasma Lipids: Women should have their cholesterol levels assessed and managed according to current clinical practice and guidelines (see Hyperlipidemia section above).

Bone Mineral Density: Monitoring of overall bone health is recommended during treatment with FEMARA. (See Musculoskeletal section above). In patients whose menopausal status is unclear or who become amenorrheic after chemotherapy, luteinising hormone (LH), follicle-stimulating hormone (FSH) and/or estradiol levels should be measured before initiating treatment with FEMARA and regularly during the first 6 months of treatment.

ADVERSE REACTIONS

Adverse Drug Reactions Overview

FEMARA (letrozole) was generally well tolerated across all studies as first-line and second-line treatment for advanced breast cancer, as adjuvant treatment of early breast cancer and as extended adjuvant treatment in women who had completed prior standard adjuvant therapy with tamoxifen. Approximately one third of the patients treated with FEMARA in the metastatic setting, and approximately 80% of the patients in the adjuvant setting (both FEMARA and tamoxifen arms, at a median treatment duration of 60 months), and extended adjuvant setting (both FEMARA and placebo arms, at a median treatment duration of 60 months) experienced adverse reactions[1]. The observed adverse reactions are mainly mild or moderate in nature, and many are associated with estrogen deprivation. The updated safety profile of FEMARA in both the adjuvant (96 months median follow-up, median treatment duration 60 months) and the extended adjuvant (62 months median follow-up, median treatment duration 60 months) settings did not reveal any new adverse reaction and was consistent with the profile reported at earlier analyses.

Adverse Events in Adjuvant Study BIG 1-98

After reviewing the results of the Primary Core Analysis, at a median treatment duration of 25 months, the independent Data and Safety Monitoring Committee, observed a difference in incidence in grade 5 myocardial infarctions (9 vs. 2 in the letrozole and tamoxifen arms, respectively) and recommended that cardiac events and certain other safety data be reviewed. Consequently, a blinded medical review of more than 2000 patients with pre-specified adverse events (Common Toxicity Criteria, CTC grade 3-5 cardiovascular events, fractures, arthritis/arthralgia, myalgia, any adverse event leading to discontinuation) or death without a prior cancer event was conducted. This medical review resulted in a change in the cause of death

[1] "Adverse reactions" defined as adverse events (AEs) suspected of being related to study treatment (including AEs with missing relationship).

for 25 patients, 19 of which were reclassified from a cardiac cause to either "sudden death, cause unknown" (9 cases in letrozole arm, 7 cases in tamoxifen arm) or to "other" (3 cases in letrozole arm). Some adverse events (such as arthritis/arthralgia and edema) reported in the primary analysis did not meet the definition of a treatment-emergent adverse event as they were present at baseline and did not worsen in severity during treatment. Patients in the BIG 1-98 study continued to be monitored by blinded medical review for cardiovascular, skeletal and endometrial events, survival status and breast cancer status as well as for events leading to discontinuation of trial treatment, throughout the trial for median treatment duration of 60 months and a median follow-up of 96 months.

Patients with other non-malignant systemic diseases (cardiovascular, renal, hepatic, lung embolism, etc.) which would prevent prolonged follow-up were ineligible for enrolment in the BIG 1-98 trial. Patients with previous DVT (deep vein thrombosis) were only included if medically suitable.

FEMARA was generally well tolerated as adjuvant treatment of early breast cancer. At the primary analysis (25 months median treatment) approximately 92% vs. 87% of the patients allocated FEMARA or tamoxifen, respectively, experienced adverse events, irrespective of suspected relationship to study drug. The most frequently reported adverse events in the adjuvant setting were hot flushes (FEMARA: 34%, tamoxifen: 38%), arthralgia/arthritis (FEMARA: 21%, tamoxifen 13%), night sweats (FEMARA: 14%, tamoxifen: 16%) and weight increased (FEMARA: 11%, tamoxifen: 13%). Most adverse events reported (81%) were grade 1 and grade 2 applying the Common Toxicity Criteria Version 2.0.

At a median treatment duration of 60 months and a median follow-up of 96 months, more than 90% of the patients in each treatment arm experienced adverse events, irrespective of suspected relationship to study drug. The observed adverse events were mainly mild or moderate in nature (a quarter of the patients in each treatment arm reported CTC grade 3 or 4 adverse events), and many events were associated with estrogen deprivation (see Clinical Trial Adverse Drug Reactions section, Table 1).
At a median treatment duration of 60 months, there was a significantly lower risk of endometrial hyperplasia or cancer with FEMARA (0.2%) than with tamoxifen (2.3%) (RR 0.11; 95% CI 0.05, 0.24). At a median follow-up of 96 months, there remained a significantly lower risk of endometrial hyperplasia or cancer with FEMARA (0.4%) than with tamoxifen (2.9%) (RR 0.15; 95% CI 0.08, 0.29). Apart from the occurrence of endometrial cancer, no major differences in the frequency of second non-breast primary malignancies were observed (see CLINICAL TRIALS section).

Adverse Events in Extended Adjuvant Study MA-17

Adverse events discussed below were analyzed irrespective of relationship to study treatment.

FEMARA was generally well tolerated as extended adjuvant treatment in women who had received prior standard adjuvant tamoxifen treatment. After a median treatment duration of 24

months for FEMARA, 87% vs. 84% of the patients on FEMARA vs. placebo experienced adverse events.

The most frequent adverse events (CTC grades 1-4), irrespective of suspected relationship to study treatment, reported during treatment by at least 2% of the patients in any treatment arm are presented in Table 2. The initial safety results, reported after a median treatment duration of 24 months, were: hot flushes (FEMARA 50% vs. placebo 43%), fatigue (lethargy, asthenia, malaise) (FEMARA 34% vs. placebo 32%), arthralgia/arthritis (FEMARA 28% vs. placebo 22%), and sweating (diaphoresis) (FEMARA 24% vs. placebo 22%). Most adverse events reported were grade 1 or grade 2 based on the Common Toxicity Criteria version 2.0. At a median treatment duration of 60 months for FEMARA, adverse events were reported for more than 90% of the patients in each treatment arm.

When the study was unblinded (at a median follow-up of 28 months), patients randomized placebo were offered to switch to FEMARA. The placebo results beyond 28 months median follow-up are confounded by the fact that 60% of patients in the placebo arm opted to switch to FEMARA, resulting in different median exposure to treatment (60 months for FEMARA, 28 months for placebo generally and 40 months for FEMARA after switch); cardiovascular and skeletal events had a median exposure of 37 months to placebo/standard care. Dates of onset were recorded for targeted adverse events of fracture, osteoporosis and cardiovascular events (including cerebrovascular and thromboembolic events). Many general adverse events were collected by check-lists without dates of onset. In most cases it cannot be determined if the adverse events in the placebo group occurred before switch to FEMARA or after switch to FEMARA. General adverse event data after unblinding of the study should be interpreted with caution. The majority of these general adverse events, however, were observed during the first year of treatment (see **ADVERSE REACTIONS**, **Clinical Trial Adverse Drug Reactions** section, Table 2, updated results).

In the updated results, hot flashes were reported significantly more often with FEMARA (61%) than with placebo (58%). Arthralgia/arthritis and myalgia tended to be reported more often with FEMARA (including in patients who switched to FEMARA) than with placebo (see also **WARNINGS AND PRECAUTIONS** section).

The risk of osteoporosis during treatment or within 30 days of stopping treatment was significantly higher for FEMARA (12.2%) than for placebo until switch (6.4%) (RR 1.90; 95% CI 1.59, 2.27). Clinical fractures were reported more often for FEMARA (10.4%) than for placebo until switch (5.8%) (RR 1.79; 95% CI 1.48, 2.17). In patients who switched to FEMARA, osteoporosis was reported in 5.4% of patients and fractures in 7.7% of patients.

Irrespective of treatment, patients ≥ 65 years at study entry experienced more bone fractures and more osteoporosis.

Updated results (median follow-up of 61 months) from the bone mineral density (BMD) substudy conducted in a subset of 219 patients (117 on FEMARA and 102 on placebo, including 77 who switched from placebo to FEMARA) showed that, at 2 years, patients receiving

FEMARA had a median decrease of 3.8% compared to baseline in hip BMD compared to 2.0% for patients receiving placebo until switch (*P*=0.02). There was no significant difference between treatments in changes in lumbar spine BMD (see Table 14). All patients should have received vitamin D and calcium supplementation. Vitamin D was not recorded. Calcium supplementation was reported for 44-66% of patients. Bisphosphonates were received by approximately a third of the patients treated with FEMARA, compared with a quarter or fewer patients in the placebo arm.

Updated results (median follow-up of 62 months) from the lipid substudy showed no significant differences between treatments in changes in total cholesterol or in any lipid fraction. The lipid substudy included 309 patients: 168 allocated FEMARA and 141 allocated placebo. In total, 94 (67%) of the patients in the placebo arm switched to FEMARA after the study was unblinded. None of the patients received lipid-lowering agents at enrolment to the substudy. Lipid-lowering agents were introduced during treatment for 22% (37/168 patients) of the patients in the randomized FEMARA arm, 21% (29/141 patients) of the patients in the placebo until switch group, and 15% (14/94 patients) of patients after switching to FEMARA (see Table 16).

In the updated analysis of cardiovascular events (including cerebrovascular and thromboembolic events) the overall incidence of events during treatment or within 30 days of stopping treatment was significantly higher for FEMARA (9.8%) than for placebo until switch (7.8%). The reported frequency of thromboembolic events was significantly higher for FEMARA (0.9%) than for placebo until switch (0.3%). The reported frequency of stroke/transient ischemic attack was also significantly higher for FEMARA (1.5%) than for placebo until switch (0.8%).

Adverse Events in First-Line and Second-Line Treatment of Advanced Breast Cancer

FEMARA (letrozole) was generally well tolerated across all studies as first-line and second-line treatment for advanced breast cancer. Approximately one third of patients treated with FEMARA in the metastatic setting experienced adverse reactions[2]. The most frequently reported adverse reactions in the clinical trials were hot flushes, nausea and fatigue. The adverse drug reactions reported from clinical trials are summarized in Tables 4 and 5 for first-line and second-line treatment with FEMARA.

<u>Clinical Trial Adverse Drug Reactions</u>

Adverse Events in Adjuvant Treatment of Early Breast Cancer in Postmenopausal Women, Median Treatment Duration 25 Months

At a median duration of treatment of 25 months, serious adverse events (SAEs) suspected to be related to study treatment were significantly less frequent with FEMARA (204/3975 patients, 5.1%) than with tamoxifen (319/3988 patients, 8.0%). Table 1 summarizes adverse events during study treatment (median duration of treatment 25 months; median follow-up 28 months). The

[2] "Adverse reactions" defined as adverse events (AEs) suspected of being related to study treatment (including AEs with missing relationship).

most frequent SAEs were thromboembolic event (FEMARA 0.6%, tamoxifen 1.7%); fracture (FEMARA 1.2%, tamoxifen 0.9%); transient ischemic attack (FEMARA 0.6%, tamoxifen 0.8%); uterine polyp (FEMARA% <0.1%, tamoxifen 0.8%); vaginal hemorrhage (FEMARA 0.1%, tamoxifen 0.7%); myocardial infarction (FEMARA 0.3%, tamoxifen 0.3%); endometrial hyperplasia (FEMARA 0%, tamoxifen 0.6%) and angina pectoris (FEMARA 0.3%, tamoxifen 0.3%).

Hypercholesterolemia determined from non-fasting laboratory evaluations was defined as an increase in total serum cholesterol in patients who had baseline values of total serum cholesterol within the normal range, and then subsequently, had an increase in total serum cholesterol of ≥ 1.5* ULN at least once. The incidence of laboratory evaluated hypercholesterolemia was more frequent in patients treated with FEMARA (5.6%) compared to tamoxifen (1.1%) (see Table 1).

FEMARA treatment was associated with a significantly higher risk of osteoporosis (2.2 vs. 1.2% with tamoxifen). Bone fractures were significantly higher in the FEMARA arm than the tamoxifen arm (6.3 vs. 4.7%, respectively) (see Table 1).

Adverse Events in Adjuvant Treatment of Early Breast Cancer in Postmenopausal Women, Median Treatment Duration 60 Months

In study BIG 1-98, at a median treatment duration of 60 months and a median follow-up of 96 months for reporting cardiovascular, skeletal and urogenital/endometrial events for patients receiving FEMARA and tamoxifen, the side effects seen were consistent with the safety profile of the drug.

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

Most adverse events reported (75%) were grade 1 and grade 2 applying the Common Toxicity Criteria (CTC) Version 2.0 / Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Table 1 summarizes adverse events during study treatment (median duration of treatment 60 months; median follow-up 96 months).

At a median duration of follow-up of 96 months, the following adverse events were reported for FEMARA and tamoxifen, respectively: bone fracture (14.7% vs 11.4%), osteoporosis (5.1% vs 2.7%), thromboembolic events (3.2% vs 4.6%), myocardial infarction (1.7% vs 1.1%), endometrial hyperplasia/endometrial cancer (0.4% vs 2.9%).

At a median duration of follow-up of 96 months, serious adverse events suspected of being related to study treatment were significantly less frequent with FEMARA (199/2448 patients, 8.1%) than with tamoxifen (270/2447 patients, 11%). The most frequent SAEs were fracture (FEMARA 2.2%, tamoxifen group (1.6%); thromboembolic event (FEMARA 0.8%, tamoxifen 1.6%); transient ischemic attack (FEMARA 1.0%, tamoxifen 1.0%); uterine polyp (FEMARA <0.1%, tamoxifen 1.2%); myocardial infarction (FEMARA 0.6%, tamoxifen 0.4%); angina

pectoris (FEMARA 0.5%, tamoxifen 0.4%); endometrial hyperplasia (FEMARA 0%, tamoxifen 0.9%); vaginal hemorrhage (FEMARA 0.2%, tamoxifen 0.9%); cataract (FEMARA 0.4%, tamoxifen 0.3%); ovarian cyst (FEMARA 0.1%, tamoxifen 0.4%) and endometrial hypertrophy (FEMARA 0%, tamoxifen 0.3%).

Table 1 Adverse events, irrespective of relationship to study treatment, reported in the adjuvant study, BIG 1-98, in 2% or more patients in any treatment arm (Safety population)

Median duration of treatment	**25 months (PCA)** [1]		**60 months (MAA)**	
Median duration of follow-up	**26 months (PCA)**		**96 months (MAA)**	
	FEMARA N=3975	**Tamoxifen N=3988**	**FEMARA N=2448**	**Tamoxifen N=2447**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
No. of patients with ≥ 1 AE gr 1-5	3659 (92.1)	3463 (86.8)	2311 (94.4)	2215 (90.5)
No. of patients with ≥ 1 AE gr 1-4	3657 (92.0)	3460 (86.8)	2309 (94.3)	2212 (90.4)
No. of patients with ≥ 1 AE gr 3-4	752 (18.9)	754 (18.9)	636 (26.0)	606 (24.8)
Vascular disorders				
Hot flashes *	1367 (34.4)	1534 (38.5)	819 (33.5)	929 (38.0)
Hypertension* [2]	131 (3.3)	121 (3.0)	138 (5.6)	139 (5.7)
Hypertension* [3]	151 (3.8)	137 (3.4)	160 (6.5)	175 (7.2)
Thromboembolic event * [2]	48 (1.2)	119 (3.0)	51 (2.1)	89 (3.6)
Thromboembolic event * [3]	58 (1.5)	128 (3.2)	79 (3.2)	113 (4.6)
General disorders				
Fatigue (lethargy, malaise, asthenia) *	348 (8.8)	352 (8.8)	235 (9.6)	250 (10.2)
Edema *	236 (5.9)	231 (5.8)	164 (6.7)	160 (6.5)
Investigations				
Weight increased	447 (11.2)	537 (13.5)	317 (12.9)	378 (15.4)
Weight decreased	185 (4.7)	169 (4.2)	140 (5.7)	129 (5.3)
Musculoskeletal and connective tissue disorders				
Arthralgia/arthritis *	804 (20.2)	519(13.0)	621 (25.4)	504 (20.6)
Myalgia *	265 (6.7)	236 (5.9)	221 (9.0)	212 (8.7)
Back pain	137 (3.4)	149 (3.7)	125 (5.1)	136 (5.6)
Bone pain	166 (4.2)	127 (3.2)	123 (5.0)	109 (4.5)
Pain in extremity	150 (3.8)	116 (2.9)	103 (4.2)	79 (3.2)
Osteopenia	41 (1.0)	27 (0.7)	87 (3.6)	76 (3.1)
Osteoporosis * [2,3]	86 (2.2)	46 (1.2)	126 (5.1)	67 (2.7)
Skin & subcutaneous tissue disorders				
Night sweats *	578 (14.5)	664 (16.6)	356 (14.5)	426 (17.4)
Alopecia	121 (3.0)	113 (2.8)	83 (3.4)	84 (3.4)
Nervous system disorders				

Table 1 Adverse events, irrespective of relationship to study treatment, reported in the adjuvant study, BIG 1-98, in 2% or more patients in any treatment arm (Safety population)

Median duration of treatment	**25 months (PCA) [1]**		**60 months (MAA)**	
Median duration of follow-up	**26 months (PCA)**		**96 months (MAA)**	
	FEMARA	**Tamoxifen**	**FEMARA**	**Tamoxifen**
	N=3975	**N=3988**	**N=2448**	**N=2447**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Headache *	148 (3.7)	139 (3.5)	105 (4.3)	94 (3.8)
Dizziness/light-headedness *	101 (2.5)	118 (3.0)	84 (3.4)	84 (3.4)
Cerebrovascular accident/ transient ischemic attack * [2]	48 (1.2)	49 (1.2)	51 (2.1)	47 (1.9)
Cerebrovascular accident/ transient ischemic attack * [3]	54 (1.4)	55 (1.4)	74 (3.4)	68 (2.8)
Metabolism & nutritional disorders				
Hypercholesterolemia *	1824 (45.9)	795 (19.9)	1280 (52.3)	700 (28.6)
Total cholesterol > 1.5*ULN [5]	174/3109 (5.6)	36/3131 (1.1)	155/1843 (8.4)	71/1840 (3.9)
Gastrointestinal disorders				
Nausea *	394 (9.9)	424 (10.6)	284 (11.6)	277 (11.3)
Constipation *	62 (1.6)	103 (2.6)	49 (2.0)	71 (2.9)
Diarrhea NOS	84 (2.1)	55 (1.4)	64 (2.6)	40 (1.6)
Vomiting *	110 (2.8)	107 (2.7)	80 (3.3)	80 (3.3)
Abdominal pain upper	61 (1.5)	50 (1.3)	59 (2.4)	43 (1.8)
Respiratory, thoracic & mediastinal disorders				
Dyspnea	89 (2.2)	90 (2.3)	68 (2.8)	77 (3.1)
Cough	64 (1.6)	82 (2.1)	48 (2.0)	62 (2.5)
Endometrial hyperplasia/cancer[2,4]	10/3090 (0.3)	62/3157 (2.0)	6/1909 (0.3)	57/1943 (2.9)
Endometrial hyperplasia/cancer[3,4]	12/3090 (0.4)	69/3157 (2.2)	11/1909 (0.6)	70/1943 (3.6)
Psychiatric disorders				
Insomnia	72 (1.8)	60 (1.5)	55 (2.2)	47 (1.9)
Depression	154 (3.9)	163 (4.1)	119 (4.9)	114 (4.7)
Reproductive system & breast disorders				
Endometrial proliferative disorders			14 (0.6)	86 (3.5)
Vaginal haemorrhage *	190 (4.8)	433 (10.9)	129 (5.3)	320 (13.1)
Vaginal irritation	145 (3.6)	124 (3.1)	112 (4.6)	77 (3.1)
Vulvovaginal dryness	111 (2.8)	73 (1.8)	88 (3.6)	41 (1.7)
Eye disorders				
Cataract	46 (1.2)	38 (1.0)	49 (2.0)	54 (2.2)
Injury, poisoning & procedural complications				
Bone fracture * [2]	252 (6.3)	187 (4.7)	249 (10.2)	175 (7.2)
Bone fracture * [3]	282 (7.1)	227 (5.7)	361 (14.7)	280 (11.4)
Neoplasms benign, malignant &				

Table 1 Adverse events, irrespective of relationship to study treatment, reported in the adjuvant study, BIG 1-98, in 2% or more patients in any treatment arm (Safety population)

Median duration of treatment	**25 months (PCA) [1]**		**60 months (MAA)**	
Median duration of follow-up	**26 months (PCA)**		**96 months (MAA)**	
	FEMARA	**Tamoxifen**	**FEMARA**	**Tamoxifen**
	N=3975	**N=3988**	**N=2448**	**N=2447**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
unspecified (including cysts & polyps)				
Second malignancies * [2]	--	--	54 (2.2)	79 (3.2)
Second malignancies * [3, 6]	76/4003 (1.9)	96/4007 (2.4)	129 (5.3)	150 (6.1)

PCA = Primary Core Analysis; MAA = Monotherapy Arms Analysis NOS = Not otherwise specified; ULN = Upper limit of normal

AEs marked * are specific target events consisting of multiple MedDRA terms

Note: Cardiovascular, skeletal, endometrial events and second malignancies were collected life-long.

[1] Based on PCA 120-day safety update

[2] During study treatment + 30 days. Median duration of treatment for PCA 120-day safety update 25 months; for MAA median is 60 months

[3] Any time after randomization. Median follow-up 28 months for PCA 120-day safety update; median 96months for MAA

[4] Excluding women who had undergone hysterectomy prior to study enrollment

[5] Denominator is patients who had baseline total cholesterol ≤ 1.5*ULN

[6] Second malignancies included as DFS events – based on original PCA analysis, median duration of follow-up 26 months; no breakdown of DFS events conducted in 120-day safety update analysis

Deaths during study treatment or within 30 days of stopping treatment due to any cause were reported for 2.2% patients in each treatment arm. Deaths due to cardiac cause were infrequent in both treatment arms (9 patients in the FEMARA arm versus 7 patients in the tamoxifen arm). Myocardial infarction was reported as cause of death for 4 patients (0.2%) treated with FEMARA compared to 1 patient (<0.1%) in the tamoxifen arm. Death from cardiac failure was reported for 3 patients treated with FEMARA and for 3 patients treated with tamoxifen. Deaths related to stroke/CVA were observed in 9 patients (5 for FEMARA, 4 for tamoxifen). There were no major differences regarding fatal thromboembolic events and deaths related to second non-breast malignancy.

In the adjuvant setting, total cholesterol levels remained relatively stable over 6 years (median 0 to 5.5% decrease) in the FEMARA arm whereas there was an expected decrease (median 10-14% decrease) over 5 years observed in the tamoxifen arm, Hypercholesterolemia recorded at least once as a check-listed adverse event was more frequent in patients treated with FEMARA (52%) compared with tamoxifen (29%). Hypercholesterolemia determined from non-fasting laboratory evaluations was defined as an increase in total serum cholesterol in patients who had baseline values of total serum cholesterol within the normal range, and then subsequently, had an increase in total serum cholesterol of ≥ 1.5* ULN at least once. The incidence of laboratory evaluated hypercholesterolemia was more frequent in patients treated with letrozole (8.4%) than with tamoxifen (3.9%) (see Table 1).

See **Adverse Events in Extended Adjuvant Treatment** below for data with respect to placebo.

Adverse Events in Extended Adjuvant Treatment of Early Breast Cancer in Postmenopausal Women, Median Treatment Duration 24 Months

At a median follow-up of 28 months, the incidence of cardiovascular events from the MA-17 core study was not significantly different between patients who received FEMARA 6.8% (175) and those who received placebo 6.5% (167). The most frequent cardiovascular events were: new or worsening angina (1.4% in the FEMARA arm vs. 1.0% in the placebo arm), myocardial infarction (0.6% in the FEMARA arm vs. 0.7% in the placebo arm), and stroke/transient ischemic attack (0.9% in the FEMARA arm vs. 0.9% in the placebo arm). These results were obtained prior to unblinding the study.

At a median follow-up of 28 months, the incidence of osteoporosis any time after randomization was higher in patients who received FEMARA (6.9%) than in patients who received placebo (5.5%) (P=0.04). The incidence of clinical fractures any time after randomization was slightly (non-significantly) higher in patients who received FEMARA than in those who received placebo (5.9% vs. 5.5% respectively). Fracture rates any time after randomization in patients with a history of osteoporosis were 10.6% in the FEMARA arm compared to 7.3% in the placebo arm; the difference is not statistically significant. In patients with a previous history of fractures, fracture rates were 12.2% in the FEMARA arm compared to 8.7% in the placebo arm; the difference is not statistically significant. These results were obtained prior to study unblinding.

Adverse Events in Extended Adjuvant Treatment of Early Breast Cancer in Postmenopausal Women, Median Treatment Duration 60 Months

Table 2 summarizes general adverse events reported in at least 2% of the patients in either treatment arm (collected during treatment) (median treatment duration 24 months for FEMARA and placebo and 60 months for FEMARA); table 3 summarizes cardiovascular and skeletal events collected life-long (including after discontinuation or completion of study treatment) in the study of FEMARA versus placebo as extended adjuvant therapy.

The median duration of extended adjuvant treatment was 60 months for patients receiving FEMARA and 28 months for placebo. The median duration of FEMARA treatment was 60 months (median follow-up 62 months) and the median duration of placebo/standard care until switch was 37 months (same median follow-up). The median duration of FEMARA treatment after switch was 40 months (median follow-up 42 months). Most adverse events reported were grade 1 or grade 2 based on the Common Toxicity Criteria Version 2.0.

Table 2 **Adverse events, irrespective of relationship to study treatment, reported at a frequency of 2% or greater in any treatment arm in study MA-17 (Safety population)**

Median treatment duration	**24 months[1]**		**60 months**
	FEMARA N=2563	**Placebo N=2573**	**FEMARA N=2567[2]**
Preferred term	**n (%)**	**n (%)**	**n (%)**
No. of patients with ≥ 1 grade 1-5 AE	2234 (87.2)	2174 (84.5)	2431 (93.7)
No. of patients with ≥ 1 grade 1-4 AE	2229 (87.0)	2170 (84.3)	2429 (94.6)
No. of patients with ≥ 1 grade 3-4 AE	419 (16.3)	389 (15.1)	672 (26.2)
Vascular disorders			
Hot flashes *	1273 (49.7)	1114 (43.3)	1564 (60.9)
Hypertension NOS	122 (4.8)	110 (4.3)	205 (8.0)
General disorders			
Fatigue (lethargy, malaise, asthenia) *	867 (33.8)	832 (32.3)	1202 (46.8)
Edema *	535 (20.9)	487 (18.9)	715 (27.9)
Chest pain	59 (2.3)	69 (2.7)	87 (3.4)
Investigations			
Weight decreased	52 (2.0)	38 (1.5)	85 (3.3)
Weight increased	55 (2.1)	51 (2.0)	75 (2.9)
Musculoskeletal and connective tissue disorders			
Arthralgia/arthritis *	709 (27.7)	570 (22.2)	1065 (41.5)
Myalgia *	243 (9.5)	173 (6.7)	455 (17.7)
Bone pain	70 (2.7)	81 (3.1)	198 (7.7)
Back pain	129 (5.0)	112 (4.4)	170 (6.6)
Pain in extremity	70 (2.7)	62 (2.4)	93 (3.6)
Osteopenia	14 (0.5)	9 (0.3)	55 (2.1)
Skin & subcutaneous tissue disorders			
Sweating (diaphoresis) *	624 (24.3)	578 (22.5)	890 (34.7)
Alopecia	112 (4.4)	83 (3.2)	161 (6.3)
Dermatitis exfoliative NOS	34 (1.3)	43 (1.7)	60 (2.3)
Rash NOS	41 (1.6)	53 (2.1)	58 (2.3)
Dry skin	42 (1.6)	49 (1.9)	62 (2.4)
Nervous system disorders			
Headache *	525 (20.5)	512 (19.9)	810 (31.6)
Dizziness/light-headedness *	365 (14.2)	344 (13.4)	568 (22.1)
Memory impairment	35 (1.4)	34 (1.3)	56 (2.2)
Metabolism and nutrition disorders			
Hypercholesterolemia *	401 (15.6)	399 (15.5)	598 (23.3)
Hypergylcemia NOS	48 (1.9)	40 (1.6)	84 (3.3)
Gastrointestinal disorders			
Nausea *	275 (10.7)	278 (10.8)	465 (18.1)
Constipation *	290 (11.3)	304 (11.8)	449 (17.5)
Diarrhea NOS	128 (5.0)	143 (5.3)	208 (8.1)
Anorexia *	119 (4.6)	96 (3.7)	195 (7.6)
Dyspepsia	72 (2.8)	82 (3.2)	136 (5.3)
Vomiting *	75 (2.9)	83 (3.2)	126 (4.9)
Abdominal pain NOS	74 (2.9)	86 (3.3)	116 (4.5)

Table 2 Adverse events, irrespective of relationship to study treatment, reported at a frequency of 2% or greater in any treatment arm in study MA-17 (Safety population)

Median treatment duration	**24 months[1]**		**60 months**
	FEMARA N=2563	**Placebo N=2573**	**FEMARA N=2567[2]**
Preferred term	**n (%)**	**n (%)**	**n (%)**
Flatulence	47 (1.8)	49 (1.9)	57 (2.2)
Respiratory, thoracic and mediastinal disorders			
Dyspnea	140 (5.5)	137 (5.3)	228 (8.9)
Cough	96 (3.7)	94 (3.7)	156 (6.1)
Psychiatric disorders			
Insomnia	149 (5.8)	120 (4.7)	232 (9.0)
Depression	115 (4.5)	104 (4.0)	174 (6.8)
Anxiety	78 (3.0)	73 (2.8)	111 (4.3)
Reproductive system and breast disorders			
Vaginal haemorrhage *	145 (5.7)	204 (7.9)	195 (7.6)
Vulvovaginal dryness	137 (5.3)	127 (4.9)	200 (7.8)
Renal and urinary disorders			
Pollakiuria	47 (1.8)	38 (1.5)	69 (2.7)
Incontinence NOS	45 (1.8)	32 (1.2)	61 (2.4)
Infections and infestations			
Infection NOS	41 (1.6)	32 (1.2)	61 (2.4)

[1] AEs after the first month of treatment

[2] Additional patients documented as having taken treatment for at least 1 day

NOS = Not otherwise specified

* Specific events that may include multiple MedDRA preferred terms

Table 3 Cardiovascular and skeletal events in the extended adjuvant study, MA-17 (Safety population)

	Initial analysis		Update
	FEMARA N=2563	Placebo N=2573	FEMARA N=2567[1]
Reporting period / event	**n (%)**	**n (%)**	**n (%)**
During treatment or within 30 days of stopping treatment			
Median duration of treatment	24 months	24 months	60 months
Cardiovascular events	143 (5.6)	139 (5.4)	251 (9.8)
Myocardial infarction	11 (0.4)	14 (0.5)	25 (1.0)
New or worsening angina	30 (1.2)	23 (0.9)	37 (1.4)
Angina requiring surgery	6 (0.2)	14 (0.5)	21 (0.8)
Thromboembolic event	10 (0.4)	6 (0.2)	23 (0.9)
Stroke/transient ischemic attack	18 (0.7)	15 (0.6)	39 (1.5)
Other	94 (3.7)	83 (3.2)	156 (6.1)
CNS/Cerebrovascular	3 (0.1)	2 (0.1)	8 (0.3)
Cardiac	24 (0.9)	20 (0.8)	53 (2.1)
Arrhythmia	40 (1.6)	48 (1.9)	70 (2.7)
Vascular	13 (0.5)	6 (0.2)	22 (0.9)
Valvular	5 (0.2)	2 (0.1)	7 (0.3)
Other	15 (0.6)	10 (0.4)	8 (0.3)
Skeletal events			
Fracture (clinical)	134 (5.2)	117 (4.5)	266 (10.4)
Patients with 1 fracture	115 (4.5)	103 (4.0)	222 (8.6)
Patients with > 1 fracture	19 (0.7)	14 (0.5)	44 (1.7)
Osteoporosis	164 (6.4)	126 (4.9)	314 (12.2)
Any time after randomization			
Median duration of follow-up	28 months	28 months	62 months
Cardiovascular events	175 (6.8)	167 (6.5)	369 (14.4)
Myocardial infarction	15 (0.6)	17 (0.7)	44 (1.7)
New or worsening angina	37 (1.4)	25 (1.0)	51 (2.0)
Angina requiring surgery	14 (0.5)	18 (0.7)	32 (1.2)
Thromboembolic event	12 (0.5)	11 (0.4)	34 (1.3)
Stroke/transient ischemic attack	23 (0.9)	22 (0.9)	68 (2.6)
Other	110 (4.3)	105 (4.1)	227 (8.8)
CNS/Cerebrovascular	3 (0.1)	3 (0.1)	10 (0.4)
Cardiac	31 (1.2)	27 (1.0)	76 (3.0)
Arrhythmia	50 (2.0)	58 (2.3)	104 (4.1)
Vascular	14 (0.5)	8 (0.3)	31 (1.2)
Valvular	5 (0.2)	2 (0.1)	11 (0.4)
Other	16 (0.6)	13 (0.5)	20 (0.8)
Skeletal events			
Fracture (clinical)	152 (5.9)	142 (5.5)	341 (13.3)
Patients with 1 fracture	129 (5.0)	121 (4.7)	276 (10.8)
Patients with > 1 fracture	23 (0.9)	21 (0.8)	65 (2.5)
Osteoporosis	176 (6.9)	141 (5.5)	373 (14.5)

[1] Additional patients documented as having taken study treatment

Note: Patients are counted once in each row but may have multiple events, so that numbers are not additive

The most frequent adverse events irrespective of drug relationship (cut-off frequency of at least 2%) reported in the 1251/2567 (49%) patients randomized FEMARA who completed 5 years of treatment were: hot flashes (823, 66%), asthenia (610, 49%), arthralgia (514, 41%), increased sweating (490, 39%), headache (425, 34%), hypercholesterolemia (367, 29%), edema NOS (337, 27%), dizziness (294, 23%) and myalgia (236, 19%).

The incidence of reported osteoporosis in the extended adjuvant study was significantly higher in patients who received FEMARA (during treatment: 12.2%; any time after randomization: 14.5%) than in those who received placebo/no treatment (during treatment: 6.4%; any time after randomization: 7.8%). Amongst women who switched from placebo to FEMARA, osteoporosis was reported by 5.4% during treatment (median duration of treatment after switching was 40 months) and 5.9% any time after randomization. During treatment, the incidence of clinical fractures was 10.4% for FEMARA compared to 5.8% for placebo. Any time after randomization, the incidence increased to 13.3% for patients in the FEMARA arm and to 7.8% for patients in the placebo arm. Amongst patients who switched from placebo to FEMARA, clinical fractures were reported for 7.7% during treatment (median duration of FEMARA after switching was 40 months), rising to 8.3% if the post treatment follow-up was included.

Irrespective of treatment, patients with a history of osteoporosis reported fractures at a higher rate than patients without such a history, as did patients with a history of bone fractures – e.g. during treatment or within 30 days of stopping treatment, fractures were reported for FEMARA in 16% of patients with a history of osteoporosis and 17% with a history of previous fractures compared with 9.5% (history of osteoporosis) and 9.9% (history of fractures) for placebo; FEMARA 9.6%, placebo 5.3% (no history of osteoporosis); FEMARA 9.5%, placebo 5.2% (no previous fractures). Amongst patients who switched from placebo to FEMARA, fractures were reported by 10% of patients with a history of osteoporosis, 7.4% for patients with no such history, and by 14.7% of patients who had previously experienced bone fractures compared with 6.8% for those without a history of fractures.

Results (median duration of FEMARA treatment was 60 months) from the MA-17 bone sub-study demonstrated that, at 2 years, compared to baseline, patients receiving FEMARA had a median decrease (versus baseline) of 3.8% versus 2.0% (P=0.022) for placebo in total hip bone mineral density. Although there was a similar reduction in lumbar spine (L2-L4) bone mineral density at 2 years (FEMARA median 3.8% decrease versus 2.0% for placebo), this difference was not statistically significant.

During study treatment or within 30 days of stopping treatment (median duration of treatment 60 months for FEMARA and 28 months for placebo), the incidence of cardiovascular events overall in study MA-17 was significantly higher for FEMARA (9.8%) than for placebo (7.0%). Most of the difference was accounted for by cerebrovascular events (FEMARA 1.5% vs. placebo 0.8%), thromboembolic events (FEMARA 0.9% vs. placebo 0.3%) and “other” cardiovascular events (FEMARA 6.1% vs. placebo 4.2%). At any time after randomization (i.e. including the post-treatment follow-up period, median duration of follow-up 62 months for FEMARA, 37 months for placebo), the overall incidence of cardiovascular events was higher in the FEMARA arm

(14.4%) than in the placebo arm (9.8%). In the FEMARA arm, there was a significantly higher reported incidence of myocardial infarction (FEMARA 1.7% vs. placebo 1.0%), thromboembolic events (FEMARA 1.3% vs. placebo 0.7%), stroke/transient ischemic attack (FEMARA 8.8% vs. placebo 6.3%) (see Table 3).

There was no significant difference between treatments in the overall number of patients dying during treatment or within 30 days of stopping treatment (FEMARA 3.0% vs. placebo 3.2%; placebo not switching 4.5%; FEMARA after switching 2.3%). There were, however, differences in cause of death: approximately twice as many patients who had received placebo died of the underlying breast cancer (placebo not switching 1.3% vs. FEMARA 0.7% and FEMARA after switching 0.6%); fatal strokes occurred in 6 cases (0.2%) in the FEMARA randomized arm and in 1 case (0.1%) after switching to FEMARA (0 cases for placebo).

During treatment or within 30 days of stopping treatment (median duration of treatment 60 months), in the randomized FEMARA arm, 1.7% of patients experienced more than one fracture, compared with 1.3% in the placebo until switch group and 2.3% in the FEMARA after switch from placebo group. Of the 120/1551 patients who experienced a fracture after switching to FEMARA from placebo, 76 patients had previously experienced a fracture on placebo (and 7 of these patients had experienced more than one fracture on placebo).

In the 77 patients who switched from placebo to FEMARA, BMD in the hip and lumbar spine showed a median decrease from baseline of approximately 1-3% at each of the first, second, third and fourth annual visits after switching to FEMARA. The median treatment duration in each group was 60 months for FEMARA, 22 months for placebo until switch and 43 months for FEMARA after switch from placebo respectively.

Results from the MA-17 lipid sub-study (median duration of FEMARA was 60 months) did not show significant differences between the FEMARA and placebo groups. Patients in the sub-study had no prior history of hyperlipidemia. As per normal clinical practice and guidelines for postmenopausal women, physicians should continue their routine monitoring of lipid levels on a regular basis.

Adverse Events in First-Line Treatment

Overall, 455 postmenopausal women with locally advanced or metastatic breast cancer were treated with FEMARA in a well-controlled clinical trial and the median time of exposure was 11 months. The incidence of adverse events was similar for FEMARA and tamoxifen. The most frequently reported adverse events were bone pain, hot flushes, back pain, nausea, arthralgia and dyspnea. Discontinuations for adverse events other than progression of tumour occurred in 10/455 (2%) of patients on FEMARA and in 15/455 (3%) of patients on tamoxifen.

Table 4 below shows the frequency of adverse reactions considered possibly related to trial drug that have been reported with an incidence of more than 2.0% (whether for FEMARA (letrozole) or for tamoxifen) in a well-controlled clinical study with FEMARA (2.5 mg daily) and tamoxifen (20 mg daily).

Table 4

Adverse Reaction **System Organ Class / Preferred term**	**FEMARA** **N= 455 (%)**	**Tamoxifen** **N=455 (%)**
Gastrointestinal Disorders		
Nausea	6.6	6.4
Constipation	2.4	1.3
Vomiting	2.2	1.5
General Disorders and Administration Site Conditions		
Fatigue	2.6	2.4
Metabolism and Nutrition Disorders		
Decreased Appetite	1.6	3.3
Increased Appetite	1.8	2.0
Nervous System Disorders		
Headache	2.2	2.4
Skin and Subcutaneous Tissue Disorders		
Alopecia	5.5	3.3
Hyperhidrosis	2.0	2.9
Vascular Disorders		
Hot Flush	16.7	14.3
Thromboembolic Events	1.5	1.9

Adverse Events in Second-Line Treatment

Table 5 below shows in decreasing order of frequency the adverse reactions - considered possibly related to trial drug according to the investigator - that have been reported with an incidence of more than 1.0% for FEMARA (letrozole) in a controlled clinical trial with FEMARA (2.5 mg daily) and megestrol acetate (160 mg daily) for up to 33 months.

Table 5

Adverse Reaction	**FEMARA** **% (N=174)**	**Megestrol Acetate** **% (N=189)**
Headache	6.9	4.8
Nausea	6.3	4.2
Peripheral edema	6.3	3.7
Fatigue	5.2	6.3
Hot flush	5.2	3.7
Hair thinning	3.4	1.1
Rash[1]	3.4	0.5
Vomiting	2.9	1.6

Adverse Reaction	FEMARA % (N=174)	Megestrol Acetate % (N=189)
Dyspepsia	2.9	1.6
Weight increase	2.3	8.5
Musculoskeletal pain[2]	2.3	1.1
Anorexia	2.3	1.1
Vaginal haemorrhage	1.7	3.2
Leukorrhea	1.7	2.6
Constipation	1.7	2.1
Dizziness	1.1	3.7
Increased appetite	1.1	3.7
Hyperhidrosis	1.1	2.1

[1] Including: erythematous rash, maculopapular rash.
[2] Including: arm pain, back pain, leg pain, skeletal pain.

There were no differences in the incidence and severity of adverse reactions in patients <55 years, 55-69 years and ≥70 years.

Post-Market Adverse Drug Reactions

Other adverse drug reactions are presented below (Table 6); some of them are reported spontaneously. Because spontaneous events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or clearly establish a causal relationship to FEMARA exposure.

Table 6 Other adverse drug reactions reported post-marketing in patients receiving FEMARA

Blood and lymphatic system disorders	Leukopenia
Cardiac disorders	Palpitations, tachycardia, ischemic cardiac events (including new or worsening angina, angina requiring surgery, myocardial infarction and myocardial ischemia), atrial fibrillation, atrial flutter, cardiac failure
Eye disorders	Cataract, eye irritation, blurred vision
Gastrointestinal disorders	Dyspepsia, abdominal pain, stomatitis, dry mouth
General disorders and administration site conditions	Pyrexia, mucosal dryness, thirst
Hepato-biliary disorders	Increased hepatic enzymes, hyperbilirubinaemia, jaundice, hepatitis
Immune system disorders	Anaphylactic reaction
Infections and infestations	Urinary tract infection
Injury, poisoning and procedural complications	Fall[1]
Investigations	Weight increased, weight decreased, increase in aminotransferases
Musculoskeletal and connective tissue disorders	Myalgia, osteoporosis, bone fractures, trigger finger
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Tumour pain[2]
Nervous system disorders	Somnolence, memory impairment, dysaesthesia (including paresthesia, hypoesthesia), dysgeusia, cerebrovascular accident, carpal tunnel syndrome
Psychiatric disorders	Anxiety (including nervousness), irritability
Renal and urinary disorders	Pollakiuria
Reproductive system and breast disorders	Vaginal discharge, breast pain
Respiratory, thoracic and mediastinal disorders	Cough
Skin and subcutaneous tissue disorders	Rash (including erythematous, maculopapular, psoriaform and vesicular rash), pruritis, dry skin, urticaria, angioedema, erythema multiforme, toxic epidermal necrolysis
Vascular disorders	Thrombophlebitis (including superficial and deep vein thrombophlebitis), hypertension, pulmonary embolism, arterial thrombosis, cerebral infarction

[1]In some post-marketing cases, fall was reported as a consequence of other adverse events such as dizziness and vertigo
[2]Tumour pain was reported only in the metastatic setting

DRUG INTERACTIONS

Drug-Drug Interactions

Drugs that may alter letrozole serum concentrations: Letrozole is mainly metabolized in the liver and the cytochrome P450 enzymes CYP3A4 and CYP2A6 mediate the metabolic clearance of letrozole. Therefore, the systemic elimination of letrozole may be influenced by drugs known to affect the CYP3A4 and CYP2A6 (see **ACTION AND CLINICAL PHARMACOLOGY** section).

A clinical interaction study with cimetidine (a non-specific inhibitor of CYP2C19 and CYP3A4) indicated that co-administration with FEMARA does not result in a clinically significant drug interaction.

Drugs that may increase letrozole serum concentrations

Inhibitors of CYP3A4 and CYP2A6 activities could decrease the metabolism of letrozole and thereby increase plasma concentrations of letrozole. The concomitant administration of strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin, and telithromycin) or strong CYP2A6 inhibitors (e.g. methoxsalen) may increase exposure to letrozole. Therefore, caution is recommended for patients administered strong CYP3A4 and CYP2A6 inhibitors.

Drugs that may decrease letrozole serum concentrations

Inducers of CYP3A4 activity could increase the metabolism of letrozole and thereby decrease plasma concentrations of letrozole. The concomitant administration of medications that induce CYP3A4 (e.g. phenytoin, rifampicin, carbamazepine, phenobarbital, and St. John's Wort) may reduce exposure to letrozole. Therefore caution is recommended in patients for whom strong CYP3A4 inducers are administered. No drug inducer is known for CYP2A6.

Co-administration of FEMARA (letrozole) and tamoxifen 20 mg daily resulted in a mean reduction of letrozole plasma levels of 37.6%. The mechanism of this interaction is unknown. (see **Use with Other Anticancer Agents** section).

Drugs that may have their systemic serum concentrations altered by letrozole: *In vitro,* letrozole inhibits the cytochrome P450 isoenzymes CYP2A6 and, moderately, CYP2C19, but the clinical relevance is unknown. Medicinal products with a narrow therapeutic index that are substrates for CYP2C19 (e.g. phenytoin, clopidogrel) should be used with caution when

administered concomitantly with letrozole. No substrate with a narrow therapeutic index is known for CYP2A6.

A clinical interaction study with warfarin (a CYP2C9 substrate) indicated that co-administration with FEMARA does not result in a clinically significant drug interaction.

A review of the clinical trial database indicated no evidence of other clinically relevant interactions with other commonly prescribed drugs.

Use with Other Anticancer Agents: Co-administration of FEMARA and tamoxifen 20 mg daily resulted in a reduction of letrozole plasma levels by 38% on average. The clinical significance of this finding has not been explored in prospective clinical trials.

There is no clinical experience to date on the use of FEMARA in combination with other anti-cancer agents.

Drug-Food Interactions

Food slightly decreases the rate of absorption (median t_{max} 1 hour fasted vs. 2 hours fed and mean C_{max} 129±20.3 nmol/L fasted vs. 98.7±18.6 nmol/L fed), but the extent of absorption (area under the curve (AUC)) remains unchanged. This minor effect on absorption rate is not considered to be of clinical relevance and therefore letrozole may be taken with or without food.

Drug-Laboratory Interactions

No clinically significant changes in the results of clinical laboratory tests have been observed.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Insufficient data available to recommend dose adjustment in patients with severe hepatic impairment (see **Hepatic impairment** section).

Recommended Dose and Dosage Adjustment

Adults: The recommended dose is one 2.5 mg tablet once daily.

In the adjuvant setting, the intended duration of treatment is 5 years

In the extended adjuvant setting, treatment with FEMARA (letrozole) is intended for 5 years and should be initiated within 3 months of completion of approximately 5 years of prior standard adjuvant tamoxifen therapy

In the first- and second-line advanced breast cancer settings, FEMARA treatment should continue until further tumour progression is evident.

Special populations

Hepatic impairment: No dose adjustment of FEMARA is required for patients with mild to moderate hepatic impairment (Child-Pugh score A or B). Insufficient data are available to recommend a dose adjustment in breast cancer patients with severe hepatic impairment (Child-Pugh C). Therefore, patients with severe hepatic impairment should be kept under close supervision for adverse events (see **WARNINGS AND PRECAUTIONS** section)

Renal impairment: No dosage adjustment is required for patients with renal impairment with a creatinine clearance (CLcr) ≥10 mL/min. Insufficient data are available in cases of renal impairment with CLcr <10 mL/min. (see **WARNINGS AND PRECAUTIONS** section).

Pediatrics (< 18 years of age): FEMARA is contraindicated in children and adolescents. The safety and efficacy of FEMARA in children and adolescents (under 18 years of age) have not been established.

Geriatrics (≥ 65 years of age): No dose adjustment is required for elderly patients.

Missed Dose

The missed dose should be taken as soon as the patient remembers. However, if it is almost time for the next dose, the missed dose should be skipped, and the patient should go back to her regular dosage schedule. Doses should not be doubled because with daily doses at 2.5 mg or above, over-proportionality in systemic exposure was observed (see **ACTION AND CLINICAL PHARMACOLOGY** section).

Administration

FEMARA should be taken orally and can be taken with or without food (see **Drug-Food Interactions** section)

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Isolated cases of FEMARA (letrozole) overdose have been reported. In these instances, the highest single dose ingested was 125 mg or 50 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. 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.

In general, treatment of overdose with letrozole should be supportive and symptomatic. Vital signs should be monitored in all patients. Complete blood count (CBC) and liver function tests should be monitored in symptomatic patients. Fluid and electrolyte status should be monitored in patients with significant vomiting and/or diarrhea. Administration of activated charcoal may be appropriate in some cases.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

FEMARA (letrozole) is a potent and highly specific non-steroidal aromatase inhibitor. It 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.

Pharmacodynamics

FEMARA exerts its anti-tumour effect by depriving estrogen-dependent breast cancer cells of one of their growth stimuli. In postmenopausal women, estrogens are derived mainly from the action of the aromatase enzyme, which converts adrenal androgens - primarily androstenedione and testosterone - to estrone (E1) and estradiol (E2). The suppression of estrogen biosynthesis in peripheral tissues and the malignant tissue can be achieved by specifically inhibiting the aromatase enzyme.

In healthy postmenopausal women, single oral doses of 0.1, 0.5 and 2.5 mg letrozole suppressed serum estrone by 75-78% and estradiol by 78% from baseline. Maximum suppression is achieved in 48-78 hours.

In postmenopausal women with advanced breast cancer, daily letrozole doses of 0.1 to 5 mg suppress estradiol, estrone and estrone sulphate plasma levels by 75-95% from baseline in all patients treated. With 0.5 mg doses and higher, many plasma levels of estrone and estrone sulphate are below the limit of detection of the assays, indicating that higher estrogen suppression is achieved with these doses. Estrogen suppression was maintained throughout treatment in all patients.

Letrozole is highly specific in inhibiting aromatase activity. Impairment of adrenal steroidogenesis has not been observed. No clinically relevant changes in the plasma levels of cortisol, aldosterone, 11-deoxycortisol, 17-hydroxy-progesterone, ACTH (adrenocorticotropic hormone) or in plasma renin activity were found in postmenopausal patients treated with 0.1 to 5

mg letrozole daily. The ACTH stimulation test performed after 6 and 12 weeks of treatment with daily doses of 0.1 to 5 mg letrozole did not indicate any attenuation of aldosterone or cortisol production. Thus, glucocorticoid or mineralocorticoid supplementation is not required.

Letrozole had no effect on plasma androgen concentrations (androstenedione and testosterone) among healthy postmenopausal women after single doses of 0.1, 0.5 and 2.5 mg, or on plasma androstenedione concentrations among postmenopausal patients treated with daily doses of 0.1 to 5 mg. These results indicate that accumulation of androgenic precursors does not occur. Plasma levels of LH and FSH are not affected by letrozole in patients, nor is thyroid function as evaluated by TSH, T_4 and T_3 uptake.

The effect of aromatase inhibitors, including FEMARA, on estrogen suppression may consequently decrease bone mineral density (BMD) and increase the rate of bone fractures and of osteoporosis. In both the adjuvant setting and extended adjuvant setting, at a median treatment duration of 60 months, a significantly higher risk of osteoporosis as well as of clinical bone fractures was seen with FEMARA compared with tamoxifen (adjuvant treatment) or placebo (extended adjuvant treatment) (see also **DETAILED PHARMACOLOGY, Human Pharmacodynamics** section).

In a bone substudy (median follow-up of 61 months) in the extended adjuvant setting, a significantly greater decrease in median total hip BMD change from baseline was seen at 2 years for FEMARA compared with placebo, but no significant changes were observed in lumbar spine BMD (see also **DETAILED PHARMACOLOGY, Human Pharmacodynamics** section).

In a study comparing 2 years of adjuvant treatment with FEMARA or tamoxifen (D2407), significant differences in favour of tamoxifen were observed over the 2 years in BMD changes from baseline (see also **CLINICAL TRIALS and DETAILED PHARMACOLOGY, Human Pharmacodynamics** sections).

In a lipid substudy (median follow-up of 62 months) in the extended adjuvant setting, no significant differences between FEMARA and placebo were observed in total cholesterol or in any lipid fraction (see also **CLINICAL TRIALS and DETAILED PHARMACOLOGY, Human Pharmacodynamics** sections).

In the adjuvant setting study comparing 2 years of treatment with FEMARA or tamoxifen, median levels of total cholesterol and LDL cholesterol remained stable with FEMARA, but decreased with tamoxifen. Consequently, total cholesterol, LDL cholesterol and the HDL:LDL ratio differed significantly between treatments in favour of tamoxifen (see also **DETAILED PHARMACOLOGY, Human Pharmacodynamics** section).

Pharmacokinetics

Absorption: Letrozole is rapidly and completely absorbed from the gastrointestinal tract (absolute bioavailability = 99.9%). Food slightly decreases the rate of absorption (median t_{max} 1

hour fasted vs. 2 hours fed and mean C_{max} 129±20.3 nmol/L fasted vs. 98.7±18.6 nmol/L fed), but the extent of absorption (area under the curve (AUC)) remains unchanged. This minor effect on absorption rate is not considered to be of clinical relevance and therefore letrozole may be taken with or without food.

Distribution: Letrozole is rapidly and extensively distributed into tissues (Vd_{SS} = 1.87 ± 0.47 L/kg). Plasma protein binding is approximately 60%, mainly to albumin. The letrozole concentration in erythrocytes is about 80% of that in plasma. After administration of 2.5 mg ^{14}C-labelled letrozole, approximately 82% of the radioactivity in plasma was unchanged compound. Systemic exposure to metabolites is therefore low.

Metabolism: Metabolic clearance to a pharmacologically inactive carbinol metabolite, CGP 44645, is the major elimination pathway of letrozole (Cl_m = 2.1 L/h), but it is relatively slow when compared to hepatic blood flow (about 90 L/h). The cytochrome P450 isoenzymes 3A4 and 2A6 were found to be capable of converting letrozole to this metabolite. With CYP3A4, the metabolism of letrozole was not saturable up to concentrations of 100 µmol/L, while with CYP 2A6 apparent saturation was observed at concentrations above 12.5 µmol/L. Formation of minor unidentified metabolites and direct renal and fecal excretion play only a minor role in the overall elimination of letrozole. Within 2 weeks after administration of 2.5 mg ^{14}C-labelled letrozole to healthy postmenopausal volunteers, 88.2 ± 7.6% of the radioactivity was recovered in urine and 3.8 ± 0.9% in feces. At least 75% of the radioactivity recovered in urine up to 216 hours (84.7 ± 7.8% of the dose) was attributed to the glucuronide of the carbinol metabolite, about 9% to two unidentified metabolites, and 6% to unchanged letrozole.

Excretion: The apparent mean terminal elimination half-life in plasma ranges from approximately 2 to 5 days. After daily administration of 2.5 mg steady-state levels are reached within 2 to 6 weeks. Plasma concentrations at steady-state are approximately 7 times higher than concentrations measured after a single dose of 2.5 mg, while they are 1.5 to 2 times higher than steady-state values 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. Since steady state levels are maintained over time, it can be concluded that no continuous accumulation of letrozole occurs.

Linearity/non-linearity

The pharmacokinetics of letrozole were dose proportional after single oral doses up to 10 mg (dose range: 0.01 to 30 mg) and after daily doses up to 1.0 mg (dose range: 0.1 to 5 mg). After a 30 mg single oral dose there was up to a 7.5-fold dose over-proportional increase in AUC value. With daily doses of 2.5 and 5 mg the AUC values increased about 3.8 and 12 fold instead of 2.5 and 5 fold, respectively, when compared to the 1.0 mg/day dose. The recommended dose of 2.5 mg/day may thus be a borderline dose at which an onset of over-proportionality becomes apparent, whereas at 5 mg/day the over-proportionality is more pronounced. The dose over-proportionality may be the result of a saturation of metabolic elimination processes.

STORAGE AND STABILITY

Protect from heat (store at room temperature 15 to 30 °C). Protect from moisture.

Keep out of reach and sight of children and pets.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each dark yellow, round, slightly biconvex tablet with bevelled edges bearing the imprint "FV" on one side and "CG" on the other, contains the medicinal ingredient letrozole (2.5 mg) and non medicinal ingredients cellulose compounds (microcrystalline cellulose and methylhydroxypropylcellulose), corn starch, iron oxide, lactose, magnesium stearate, polyethylene glycol, sodium starch glycolate, silicon dioxide, talc and titanium dioxide.

Available in blister packages containing 30 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

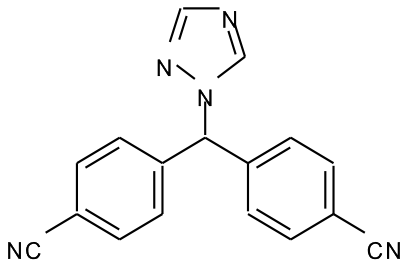
Proper name: Letrozole

Chemical name: 4,4'-[(1*H*-1,2,4-triazol-1-yl) methylene] bis-benzonitrile

Molecular formula: $C_{17}\ H_{11}\ N_5$

Molecular mass: 285.3

Structural formula:



Solubility:

Solvent	Temperature	Solubility
Water	25°C	0.144 mmol/L
Water	37°C	0.235 mmol/L
0.1N HCl	25°C	0.26 mmol/L
0.1N HCl	37°C	0.428 mmol/L
0.067 M Phosphate buffer	25°C	0.123 mmol/L
Simulated intestinal fluid	37°C	0.218 mmol/L
Dichloromethane	25°C	410-440 mmol/L
96% Ethanol	25°C	21-23 mmol/L
Methanol	25°C	40-50 mmol/L
Toluene	25°C	6-7 mmol/L

Melting range: 184-185 °C

pK value: 0.7 ± 0.2 in water at 22°C (triazole)

CLINICAL TRIALS

Adjuvant Treatment of Early Breast Cancer in Postmenopausal Women, Study BIG 1-98

In a multi-centre, double-blind study (BIG 1-98) in the adjuvant setting, enrolling over 8,000 postmenopausal women with resected, receptor-positive early breast cancer, patients were randomly allocated one of the following treatments:

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

The primary endpoint of this trial was disease-free survival (DFS) (i.e. interval between randomization and earliest occurrence of a local, regional, or distant recurrence, or invasive contralateral breast cancer, second primary cancer, or death from any cause). The secondary endpoints were overall survival (OS), systemic disease-free survival (SDFS), invasive contralateral breast cancer, distant disease-free survival (DDFS), time to breast cancer recurrence (TBR) and time to distant metastasis (TDM).

The Primary Core Analysis (PCA) included patients in all treatment arms, but follow-up in the two sequencing arms was truncated to 30 days after the switch in treatments. The original PCA analysis was conducted at a median treatment duration of 24 months and a median follow-up of 26 months (Table 8 and Figures 1 and 2). In 2005, based on the original PCA data showing a significant advantage in DFS with FEMARA compared with tamoxifen (HR 0.81; 95% CI 0.70, 0.93; *P*=0.003) (Table 8) and on the recommendations of the independent Data Monitoring Committee, the protocol was amended, the tamoxifen arms were unblinded and patients were allowed to cross over to FEMARA to complete their adjuvant therapy if tamoxifen had been given for 2 to 4.5 years, or to start extended adjuvant therapy if tamoxifen had been given for at least 4.5 years. In total, 632 (26%) patients opted to cross to FEMARA, 448 patients to complete adjuvant therapy and 184 to start extended adjuvant therapy. (These 184 patients include 12 women who crossed to another aromatase inhibitor.)

The design of the PCA is not optimal to evaluate the effect of FEMARA after a longer time because follow-up was truncated in two arms at around 25 months. The Monotherapy Arms Analysis (MAA), despite the confounding of the tamoxifen reference arm by a selective crossover to FEMARA, provides the comparison of 5 years of FEMARA monotherapy compared to tamoxifen monotherapy (Table 9). Approximately 7% of the total patient-years follow-up time in the tamoxifen-alone arms was affected by the selective crossover in the MAA.

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

Table 7 Selected Study Population Demographics for Adjuvant Study (ITT population)

Characteristic	Primary Core Analysis (PCA)		Monotherapy Arms Analysis (MAA)	
	FEMARA N=4003 (%)	Tamoxifen N=4007 (%)	FEMARA N=2463 (%)	Tamoxifen N=2459 (%)
Age (median, years)	61	61	61	61
Age range (years)	38-89	39-90	38-88	39-90
Hormone receptor status (%)				
ER+ and/or PgR+	99.7	99.7	99.7	99.7
Both unknown	0.3	0.3	0.3	0.3
Nodal status (%)				
Node negative	52	52	50	52
Node positive	41	41	43	41
Nodal status unknown	7	7	7	7
Prior adjuvant chemotherapy	24	24	24	24
Race				
White / Caucasian	97.4	97.6	97.6	98.2
Black	0.3	0.1	0.2	<0.1
Asian	0.4	0.4	0.5	0.4
Other / Missing	1.9	1.8	1.6	1.3

PCA Efficacy Results

Data in Table 8 and Figures 1 and 2 reflect results of the Primary Core Analysis (PCA) including data 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). Data in Table 8 report results of the PCA at both 26 months and 60 months median follow-up, respectively.

In the initial analysis, conducted after a median follow-up of 26 months, the estimated 5-year DFS rates were 84.0% for FEMARA and 81.4% for tamoxifen.

Table 8 Disease-free and overall survival (PCA ITT population) at a median follow-up of 26 months and of 60 months

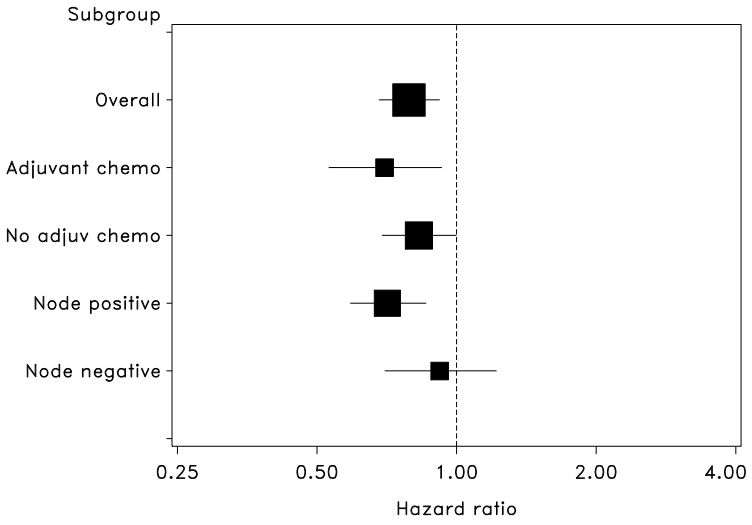
Endpoint	Original PCA Median follow-up 26 months Median treatment 24 months Hazard ratio (95% CI);	Updated PCA Median follow-up 60months* Median treatment 32 months Hazard ratio (95% CI);
DFS [1]	0.81 (0.70, 0.93); *P*=0.003	0.86 (0.77, 0.96); *P*=0.008
DFS excluding second primaries	0.79 (0.68, 0.92); *P*=0.002	0.85 (0.76, 0.96); *P*=0.008

Table 8 Disease-free and overall survival (PCA ITT population) at a median follow-up of 26 months and of 60 months

Endpoint	Original PCA Median follow-up 26 months Median treatment 24 months Hazard ratio (95% CI);	Updated PCA Median follow-up 60months* Median treatment 32 months Hazard ratio (95% CI);
Time to distant metastases[2]	0.73 (0.60, 0.88)	0.79 (0.68, 0.92)
DDFS[3]	0.82 (0.70, 0.97)	0.84 (0.74, 0.95)
SDFS[4]	0.83 (0.72, 0.97)	0.87 (0.77, 0.98)
Contralateral breast cancer (invasive)	0.61 (0.35, 1.08)	0.76 (0.50, 1.15)
OS	0.86 (0.70, 1.06)	0.87 (0.75, 1.01)

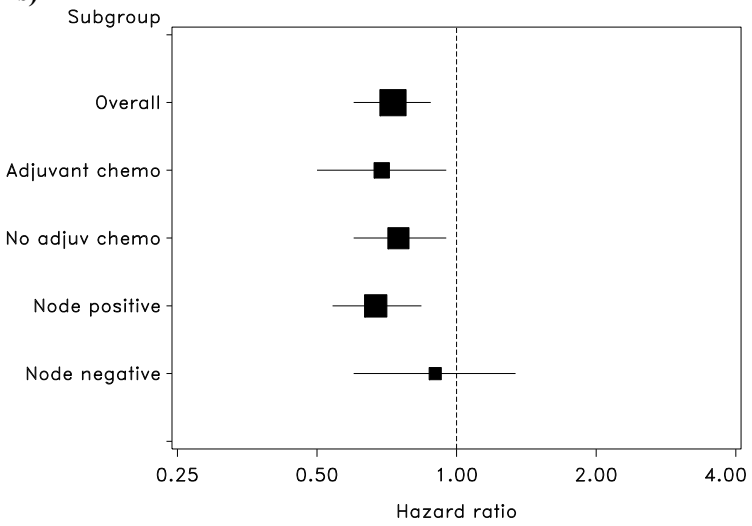
[1] DFS events: Loco-regional recurrence, distant metastasis, invasive contralateral breast cancer, second non-breast primary cancer or death without prior cancer event, from any cause
[2] Risk of distant metastases only.
[3]Distant disease-free survival events: Earlier event of either distant metastasis or death from any cause
[4] Systemic disease-free survival events: Same as protocol definition, but excluding all breast events
*Note: At original analysis, median duration of treatment was 24 months. In the updated analysis, the two sequencing treatment arms were truncated 30 days after the switch (at approximately 2 years), while in the monotherapy arms, median treatment duration was 60 months. Overall, the truncation in two arms brought the median duration of treatment to approximately 32 months.

Figure 1 Forest plot for DFS by subgroup (median follow-up of 26 months)



Favours FEMARA Favours Tamoxifen

Figure 2 **Forest plot for time to distant metastasis by subgroup (median follow-up of 26 months)**



Favours FEMARA Favours Tamoxifen

Boxes show hazard ratios and whiskers show 95% confidence intervals. Size of boxes is proportional to number of events.

MAA Efficacy Results

The Monotherapy Arms Analysis (MAA) comparing the efficacy of FEMARA monotherapy to tamoxifen monotherapy at a median duration of treatment of 5 years and a median follow-up of 96 months is presented in Table 9.

Table 9 **Key efficacy results at a median duration of 60 months and a median follow up of 96 months (MAA ITT population)**

	FEMARA N=2463	**Tamoxifen N=2459**	**Hazard ratio (95% CI)**	***P* value [1]**
Disease-free survival (primary)				
Events (protocol definition) [2]	626	698	0.87 (0.78, 0.97)	0.01
5-year DFS rate (%)	85.5	82.5		
Events (excluding second non-breast primary malignancies)	552	619	0.87 (0.77, 0.97)	0.01
5-year DFS rate (%)	87.4	84.7		
Overall survival (secondary)				
Number of deaths	393	436	0.89	

	FEMARA N=2463	Tamoxifen N=2459	Hazard ratio (95% CI)	*P* value [1]
			(0.77, 1.02)	
Distant metastasis (secondary)	301	342	0.86 (0.74, 1.01)	
Distant disease-free survival (secondary)	477	525	0.89 (0.78, 1.01)	
Systemic disease-free survival (secondary)				
Protocol definition	571	625	0.89 (0.80, 1.00)	
Excluding second non-breast primary malignancies	496	544	0.89 (0.79, 1.01)	
Contralateral breast cancer (invasive) (secondary)	45	71	0.62 (0.43, 0.90)	

[1] Logrank test, stratified by randomization option and use of chemotherapy (yes/no)

[2] DFS events: loco-regional recurrence, distant metastasis, invasive contralateral breast cancer, second (non-breast) primary malignancy, death from any cause without a prior cancer event

Adjuvant Treatment of Early Breast Cancer in Postmenopausal Women, Study D2407 (see also DETAILED PHARMACOLOGY section)

Study D2407 was a phase III, open-label, randomized, multi-centre study designed to compare the effects of adjuvant treatment with letrozole to tamoxifen on bone mineral density (BMD), bone markers and fasting serum lipid profiles. In total, 263 postmenopausal women with hormone sensitive resected primary breast cancer were randomly assigned either FEMARA 2.5 mg daily for 5 years or tamoxifen 20 mg daily for 2 years followed by 3 years of FEMARA daily.

The primary objective was to compare the effects on lumbar spine (L2-L4) BMD of letrozole versus tamoxifen, evaluated as percent change from baseline lumbar spine BMD at 2 years. (assessment by central review, based on dual X-ray absorptiometry, DXA).

At 24 months, the lumbar spine (L2-L4) BMD showed a median decrease of 4.1% in the letrozole arm compared to a median increase of 0.3% in the tamoxifen arm (difference = 4.4%) a statistically significant difference in favour of tamoxifen ($P<0.0001$). Significant differences in favour of tamoxifen were noted irrespective of category of initial T-score.
At 24 months, total hip BMD showed a median decrease of 3.0% from baseline with FEMARA compared to a median increase of 1.2% for tamoxifen (difference = 4.2%, a significant difference). Significant differences in favour of tamoxifen were noted irrespective of category of initial T-score.

Significantly more patients receiving FEMARA than tamoxifen were found by central review to have had a decrease of 8% or greater from baseline over 2 years in lumbar spine BMD (FEMARA, 15.5%; tamoxifen, 1.0%) or in total hip BMD (FEMARA, 7.8%; tamoxifen, 3.1%). During the 2 year period, fractures were reported (central review, treatment-blinded) for 20 patients (15%) in the FEMARA arm, and 22 patients (17%) in the tamoxifen arm. Of these, 7 patients (5%) in each treatment arm had clinical fractures. There was no significant difference between treatments in fracture rate. All patients should have received vitamin D and calcium supplementation. Post baseline bisphosphonates were given in 14% of patients treated with FEMARA, 5% of those treated with tamoxifen.

At 5 years, in the FEMARA arm, there was a median decrease of 5.66% from baseline in the lumbar spine BMD (n=56) and a median decrease of 5.77% in total hip (n=62). There was a general shift downwards in T-score over the 5 years. Amongst patients whose DXA readings were centrally evaluated and who had received bisphosphonate therapy, for lumbar spine and total hip normal T-scores (> 1.0), there were 51 patients each at baseline and 39 and 47, respectively, at 5 years. For lumbar spine and total hip osteopenic T-scores (≤ -1.0 and > -2.5), there were 5 and 11 patients, respectively, at baseline and 17 and 15, respectively, at 5 years. No patient with a normal BMD (normal T score) at baseline became osteoporotic during 5 years as evaluated by central review. One patient evaluated as having osteopenia at baseline (T score of -1.9) was diagnosed with osteoporosis during the treatment period by central review, despite unevaluable T-scores in L2-L4 (due to severe degenerative disk disease) and hip T-scores that remained higher than -2.5 at all times. Over the 5-year study, 37% of patients treated with FEMARA received bisphosphate therapy, including 18% of patients who started bisphosphonate therapy after initiating treatment with FEMARA.

Tamoxifen is known to decrease total cholesterol and particularly, LDL cholesterol. Over the first 2 years of the study, median LDL cholesterol levels remained stable for FEMARA, but decreased by up to 28% for tamoxifen. Median HDL cholesterol levels remained relatively stable over the 2 years in both treatment arms, giving rise to significant differences in favour of tamoxifen in the HDL:LDL ratio. No significant treatment differences were observed in triglyceride levels. Clinically relevant changes in total cholesterol at 2 years occurred significantly more often for patients treated with FEMARA (17%) than with tamoxifen (5%). Significantly more patients receiving FEMARA received lipid lowering agents (20%) than receiving tamoxifen (8%). Dietary measures for reducing lipids were reported for 4% of patients in each treatment arm. At 5 years, on the FEMARA arm, 23% of patients experienced clinically relevant changes in total cholesterol.

At 2 years, significantly more patients treated with FEMARA received lipid-lowering drugs (20%) than patients treated with tamoxifen (8%). Dietary control of lipids occurred equally often in both treatment arms (4%). Lipid-lowering agents were generally introduced when total cholesterol values rose above 6 mmol/L. At 5 years, on the FEMARA arm, 32% of patients received lipid lowering drugs.

Extended Adjuvant Treatment of Early Breast Cancer in Postmenopausal Women

The MA-17 (CFEM345G MA-17) trial was a multi-centre, double-blind, randomized, placebo-controlled phase III trial, performed in over 5100 postmenopausal women with receptor-positive (or unknown) primary breast cancer. Patients who had remained disease-free after completion of adjuvant treatment with tamoxifen (4.5-6 years) were randomly assigned either FEMARA 2.5 mg daily or placebo for 5 years.

Disease-free survival (DFS) was the primary endpoint, defined according to the study protocol as the time from randomization to the earliest event of time to recurrence of the primary disease (i.e. loco-regional recurrence or distant metastasis) or development of contralateral breast cancer (i.e. breast cancer recurrence). (The protocol definition excluded deaths.) Secondary endpoints included: overall survival (OS), time to distant metastasis, contralateral breast cancer, and other clinical and laboratory safety parameters.

Following review of the results of the first planned interim analysis, conducted after a median follow-up of 28 months and a median treatment duration of 24 months, in light of the statistically significant benefit in DFS in favour of FEMARA, the study was unblinded and women who were disease-free in the placebo arm were allowed to switch to FEMARA for up to 5 years. MA-17 transformed into an open-label, observational, non-randomized study, with a substantial impact on the subsequent safety and efficacy results.

Updated analyses were conducted at a median overall follow-up of 62 months and median duration of treatment in the randomized FEMARA arm of 60 months. 48.7% of the patients in the original randomized letrozole arm have completed 5 years of extended adjuvant treatment with letrozole. Following study unblinding, 1551 women (60% of those eligible to switch) switched from placebo to FEMARA at a median 31 months after completion of adjuvant tamoxifen therapy (range 12-106 months). Subsequent patient-years of follow-up under FEMARA after switch account for 64% of the total years of follow-up in the randomized placebo arm. Median duration of follow-up in the FEMARA after switch group was 42 months and median duration of FEMARA treatment after switch was 40 months. Following study unblinding, open-label FEMARA was continued in the randomized FEMARA arm and was given to those women who opted to switch from placebo to FEMARA. In patients who opted not to switch, placebo was no longer dispensed – these women received standard care (i.e. observation). Median duration of placebo/standard care (up until any switch to FEMARA that may have occurred) was 37 months.

Selected baseline characteristics for the study population are shown in Table 10.

Table 10 Selected study population demographics (ITT population)

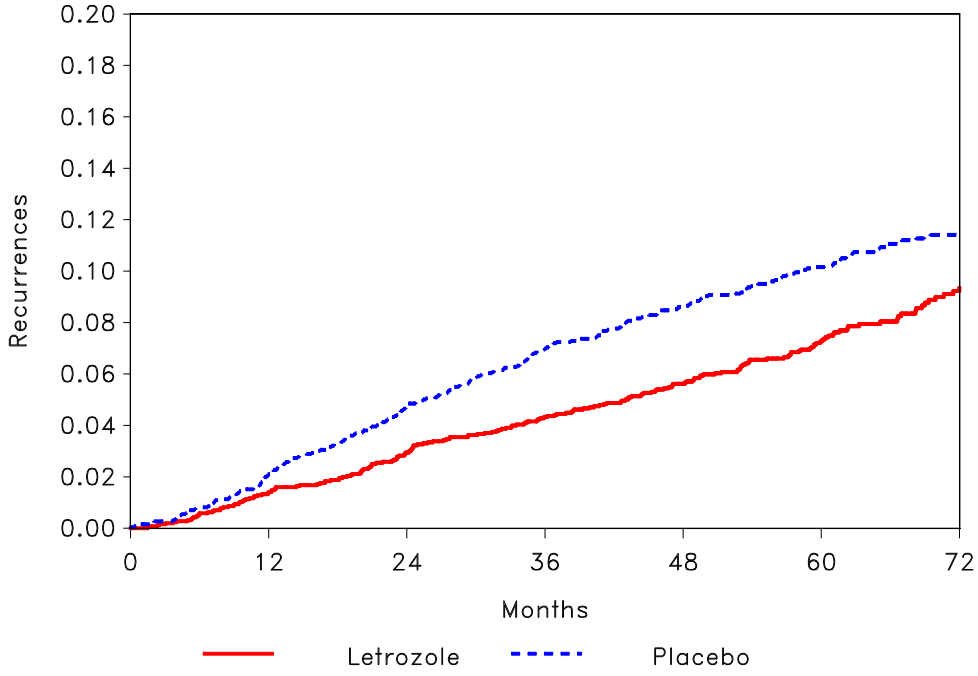
Baseline status	**FEMARA N=2583**	**Placebo N=2587**
Age: Median (years) at enrolment	62	62
Minimum-maximum (years)	32-90	34-94
< 65 years at enrolment (%)	58	60
≥ 65 years at enrolment (%)	42	40
Race (%)		

Table 10 Selected study population demographics (ITT population)

Baseline status	FEMARA N=2583	Placebo N=2587
Caucasian	88	90
Black	3.2	3.5
Oriental	1.8	0.9
Other	6.5	5.2
Hormone receptor status (%)		
Node negative	50	50
Node positive	46	46
Nodal status unknown	4	4
Chemotherapy (%)	46	46

Note: Prior treatment with tamoxifen in both arms ranged from 4.5 to 6 years, with a median duration of 5 years

Figure 3 Time to breast cancer recurrence (MA-17 protocol definition of DFS event) in updated analysis



Note: Switches in the placebo arm to FEMARA are ignored.

Tables 11 and 12 show disease-free and overall survival with subset analysis by receptor status, nodal status and previous chemotherapy at median follow-up of 28 months and 62 months.

In the primary analysis (conducted at a median follow-up of 28 months), FEMARA was shown to reduce the risk of breast cancer recurrence (protocol definition of DFS) by 42% compared with placebo (hazard ratio 0.58; 95% CI 0.45, 0.76; *P*=0.00003). Subgroup sensitivity analysis confirmed the robustness of the data. The statistically significant benefit in DFS in favour of FEMARA was observed regardless of nodal status (node negative, hazard ratio 0.48; 95% CI 0.30, 0.78; *P*=0.002; node positive, hazard ratio 0.61; 95% CI 0.44, 0.83; *P*=0.002).

The risk of distant metastases was significantly lower with FEMARA than with placebo (hazard ratio 0.61; 95% CI 0.44, 0.83; *P*=0.003).

The risk of developing contralateral breast cancer was also substantially reduced with FEMARA compared with placebo (40% reduction in the risk) although the difference between treatments was not statistically significant (*P*=0.12).

Overall survival did not show significant differences between treatments; relatively few deaths had occurred at the time of the analysis. Subgroup analysis indicated a more pronounced benefit in node positive patients (hazard ratio 0. 61, 95% CI 0.38, 0.97). In node-negative patients, there was an increase in the number of deaths in the FEMARA arm (19/1298 patients, 1.5%) compared with the placebo arm (14/1301 patients, 1.1%) (hazard ratio 1.36; 95% CI 0.68, 2.71).

The updated final analysis, conducted at a median follow-up of 62 months, confirmed the significant reduction in the risk of recurrence of the primary disease with FEMARA compared with placebo. For time to distant metastases and overall survival, however, there was no significant difference between treatments. In addition, in the subgroup of patients with node negative disease, an increase in the number of deaths was observed in the FEMARA arm (90/1298 patients, 6.9%) compared with the placebo arm (79/1301 patients, 6.1%) (hazard ratio 1.34; 95% CI 0.99, 1.81). There was no difference between treatments in the risk of death in patients with node-positive disease (FEMARA 128/1184 patients, 10.8%; placebo 145/1187 patients, 12.2%; hazard ratio 0.96; 95% CI 0.75, 1.29). Figures 4 and 5 show Kaplan-Meier curves for the overall population for the node-negative and node-positive subgroups. All updated analyses were affected by the confounding effects of around 60% of the patients in the placebo arm switching to FEMARA when the study was unblinded.

Table 11 Disease-free survival, time to distant metastases, contralateral breast cancer and overall survival (Modified ITT population)

	2004 primary analysis – median follow-up 28 months			**2008 updated analysis[1] – median follow-up 62 months**		
	Letrozole	**Placebo**	**HR (95% CI)[2]**	**Letrozole**	**Placebo**	**HR (95% CI)[2]**
	N=2582	**N=2586**	***P* value**	**N=2582**	**N=2586**	***P* value**
Disease-free survival (protocol definition)[3]						
Events	92 (3.6%)	155 (6.0%)	0.58 (0.45, 0.76) 0.00003	209 (8.1%)	286 (11.1%)	0.75 (0.63, 0.89) 0.001
4-year DFS rate	94.4%	89.8%		94.4%	91.4%	
Disease-free survival including deaths from any cause						
Events	122 (4.7%)	193 (7.5%)	0.62 (0.49, 0.78) 0.00003	344 (13.3%)	402 (15.5%)	0.89 (0.77, 1.03) 0.120
5-year DFS rate	90.5%	80.8%		88.8%	86.7%	

	2004 primary analysis – median follow-up 28 months			2008 updated analysis[1] – median follow-up 62 months		
	Letrozole	Placebo	HR (95% CI)[2]	Letrozole	Placebo	HR (95% CI)[2]
	N=2582	N=2586	*P* value	N=2582	N=2586	*P* value
Time to distant metastases						
Events	57 (2.2%)	93 (3.6%)	0.61 (0.44, 0.84) -	142 (5.5%)	169 (6.5%)	0.88 (0.70, 1.10) -
Overall survival						
Deaths	51 (2.0%)	62 (2.4%)	0.82 (0.56, 1.19) -	236 (9.1%)	232 (9.0%)	1.13 (0.95, 1.36) -
Contralateral breast cancer						
Invasive	15 (0.6%)	25 (1.0%)	0.60 (0.31, 1.14) -	33 (1.3%)	51 (2.0%)	0.644 (0.41, 1.00) -

HR = Hazards ratio; CI = Confidence Interval

[1] When the study was unblinded in 2003, 1551 patients in the randomized placebo arm (60% of those eligible to switch – i.e. who were disease-free) switched to letrozole at a median 31 months after randomization. The analyses presented here ignore the switching under the ITT principle.

[2] Stratified by receptor status, nodal status and prior adjuvant chemotherapy.

[3] Protocol definition of disease-free survival events: loco-regional recurrence, distant metastasis or contralateral breast cancer.

[4] Odds ratio and 95% CI for the odds ratio.

Table 12 Disease-free and overall survival by receptor status, nodal status and previous chemotherapy (Modified ITT population)

	2004 analysis – median follow-up 28 months		2008 analysis – median follow-up 62 months[1]	
	HR (95% CI)[2]	*P* value	HR (95% CI)[2]	*P* value
Disease-free survival (protocol definition)				
Receptor status positive	0.57 (0.44, 0.75)	0.00003	0.74 (0.62, 0.89)	0.001
Nodal status				
Negative	0.48 (0.30, 0.78)	0.002	0.67 (0.49, 0.93)	0.015
Positive	0.61 (0.44, 0.83)	0.002	0.78 (0.62, 0.97)	0.027
Chemotherapy				
None	0.58 (0.40, 0.84)	0.003	0.71 (0.54, 0.92)	0.010
Received	0.59 (0.41, 0.84)	0.003	0.79 (0.62, 1.01)	0.055

	2004 analysis – median follow-up 28 months		2008 analysis – median follow-up 62 months[1]	
	HR (95% CI)[2]	***P* value**	**HR (95% CI)[2]**	***P* value**
Overall survival				
Nodal status				
Negative	1.36 (0.68, 2.71)	-	1.34 (0.99, 1.81)	-
Positive	0.61 (0.38, 0.97)	-	0.96 (0.75, 1.21)	-

HR = Hazards ratio; CI = Confidence Interval

[1] Including 60% of eligible patients who switched from placebo to letrozole after the study was unblinded in 2003

[2] From Cox regression models

Figure 4 Overall survival (Time to death) - Randomised treatment group regardless of switch (Modified ITT population)

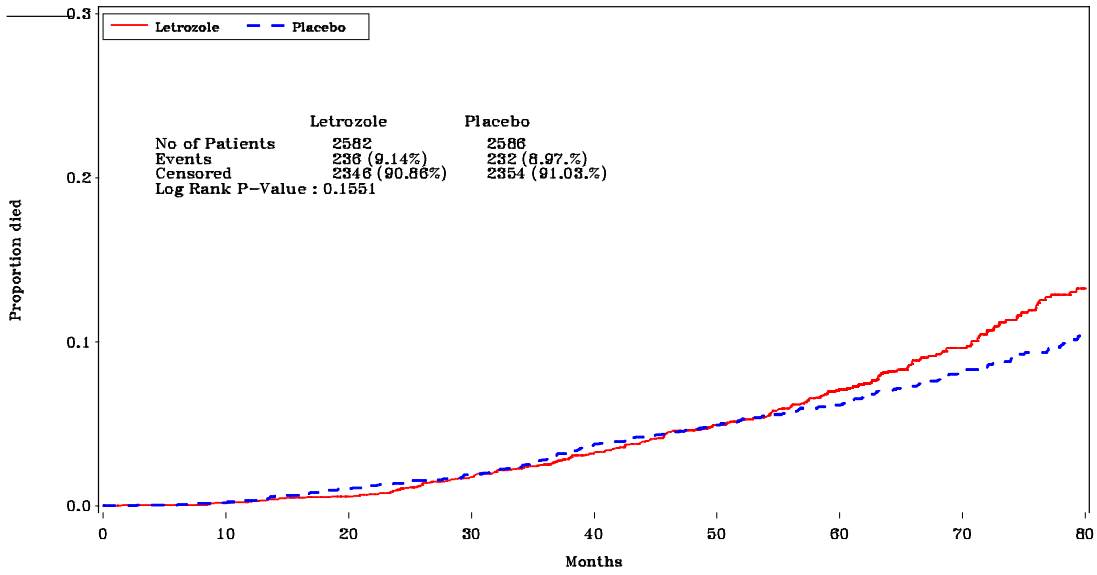
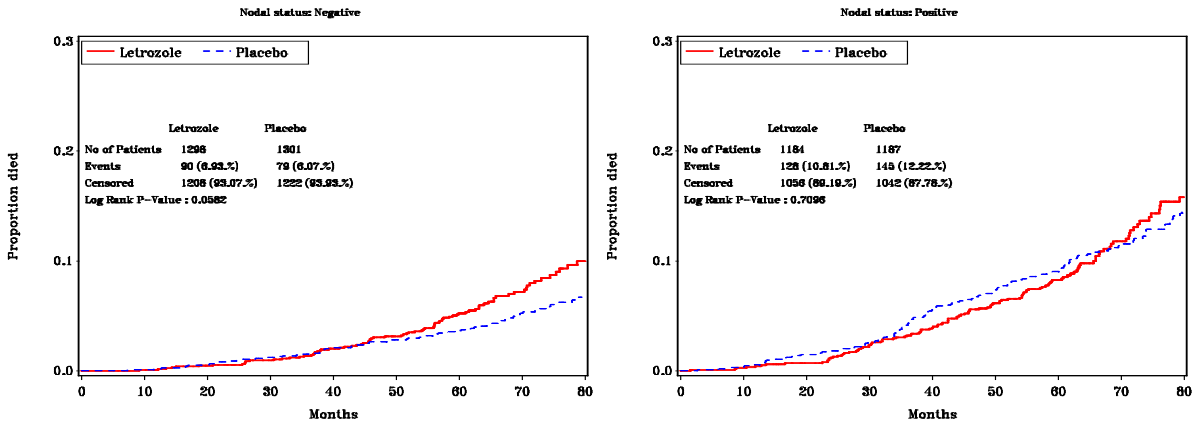


Figure 5 **Overall survival (Time to death) by nodal status - Randomised treatment group regardless of switch (Modified ITT population)**



Health related quality of life was also assessed in the MA-17 study using the SF-36 Health Survey Questionnaire as well as the MENQOL, a quality of life scale specifically addressing menopausal symptoms. The SF-36 instrument has 36 questions, which yield two summary scores: physical and mental health summary measures. In the initial analysis, no significant differences were observed in global physical or mental summary scores. Treatment differences in favour of placebo were observed in assessments by patients particularly in the measures of physical functioning, bodily pain, vitality, sexual and vasomotor items.

In the updated analysis of quality of life, restricting the analysis to women who had received FEMARA or placebo/no treatment for at least 3 years, there were no significant differences between treatments in physical component summary score or mental component summary score, or in any domain score (physical health; role function-physical; bodily pain; general health; vitality; social function; role function-emotional; or mental health – all SF-36 scale). There was no significant difference from baseline between treatments in any domain on the specific menopausal symptoms scale (MENQOL) (vasomotor; psychological; physical or sexual).

Considering all women in the sub-study and looking at the individual symptoms of the MENQOL scale, significantly more women who received FEMARA than who received placebo/no treatment were most bothered (generally in the first year of treatment) by those symptoms deriving from estrogen deprivation – hot flashes and vaginal dryness. The symptom that bothered most patients in both arms (but significantly more in the FEMARA arm than in the placebo arm) was aching muscles.

First-Line Treatment

One large, randomized, well-controlled, multinational, double-blind Phase III trial was conducted in 907 postmenopausal patients with locally advanced or metastatic breast cancer. Patients were randomized to FEMARA 2.5 mg daily or tamoxifen 20 mg daily.

Time to progression (TTP) was the primary endpoint of the trial. In 907 women, FEMARA was superior to tamoxifen in TTP (P<0.0001). Median TTP was 9.4 months for FEMARA versus 6.0 months for tamoxifen. FEMARA was also superior to tamoxifen in secondary endpoints consisting of overall objective tumour response [Complete Response (CR) + Partial Response (PR)], time to treatment failure (TTF) and clinical benefit (CR+PR+NC ≥ 24 weeks). Objective response rate (ORR) was statistically significant (P=0.0002) for FEMARA as compared to tamoxifen: 32% of patients in the FEMARA arm achieved a confirmed response (CR, 9%; PR, 23%; 95% CI for ORR 28 to 36 %), compared with 21% (CR, 3%; PR, 18%; CI for ORR 17 to 25%) in the tamoxifen arm. Median duration of objective tumour response was 25 months for FEMARA (95% CI 21 to 36 months) compared with a median 23 months for tamoxifen (95% CI 20 to 26 months). Although the difference was not statistically significant (*P*=0.0578), the difference favoured FEMARA. The hazard ratio comparing the subsequent risk of progression in responding patients treated with FEMARA to the risk in responding patients treated with tamoxifen was 0.74 (95% CI 0.54 to 1.01), *P*=0.0578. In addition to a significantly higher response rate with FEMARA, where response occurred, the subsequent risk of progression was reduced by 26% with FEMARA compared to the risk with tamoxifen (hazard ratio 0.74; 95% CI for the hazard ratio: 46% reduction in the subsequent risk of progression with FEMARA to 1% increase in the subsequent risk of progression with FEMARA compared with tamoxifen in responding patients).

TTF was statistically significant for FEMARA as compared to tamoxifen (P<0.0001). Median TTF was 9.0 months for FEMARA versus 5.7 months for tamoxifen. Clinical benefit was statistically significant for FEMARA when compared to tamoxifen (50% vs. 38%, P=0.0004).

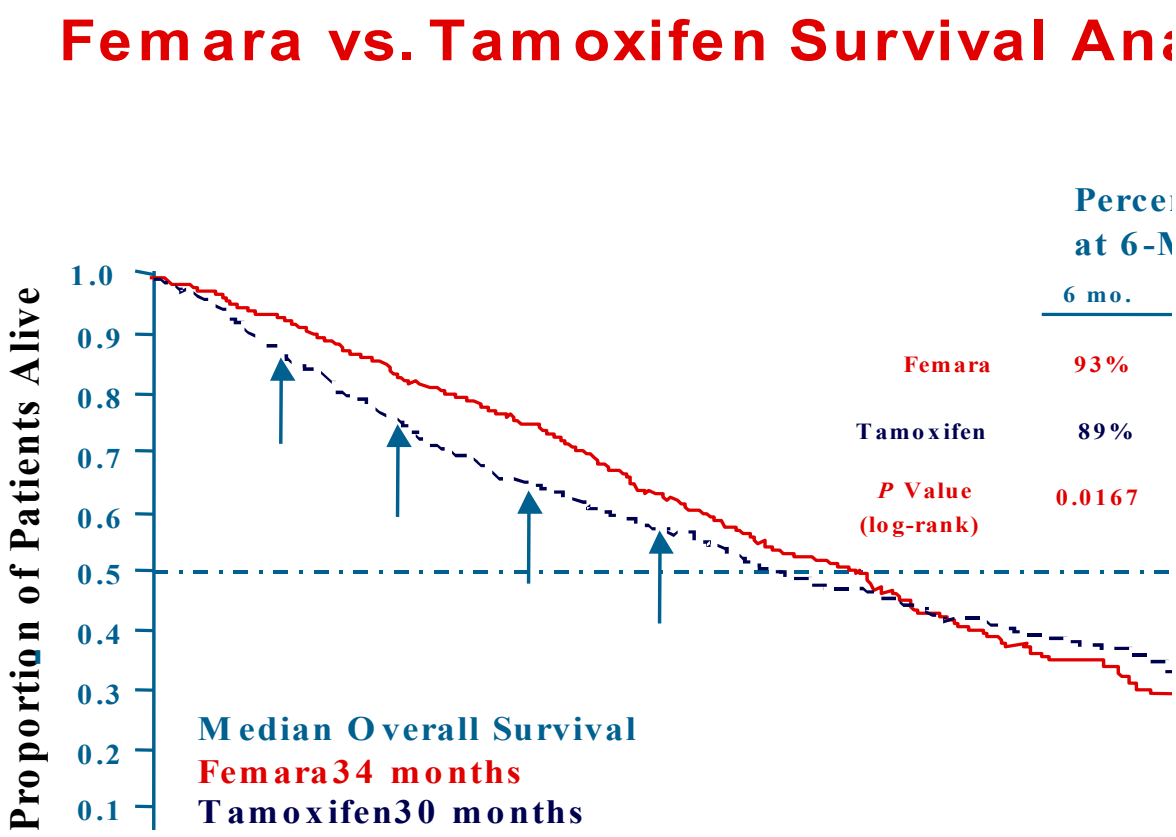
Data from this trial were further analyzed to determine the impact of prior adjuvant tamoxifen therapy on TTP. The superiority of FEMARA was observed in the sub-group of patients who received no prior adjuvant tamoxifen therapy. Patients treated with letrozole had a median TTP of 9.5 months (n=369) vs. 6.0 months for tamoxifen-treated patients (n=371), P=0.0003. Similar results were seen in those patients who had received prior adjuvant tamoxifen. The median TTP for letrozole-treated patients was significantly longer at 8.9 months (n=84), vs. the tamoxifen-treated group at 5.9 months (n=83), P=0.0033. Treatment with FEMARA lead to a significantly longer TTP compared with tamoxifen, irrespective of whether patients had received prior adjuvant therapy.

Sub-group analysis was also performed on the Objective Response Rate (CR+PR). Patients who received no prior adjuvant tamoxifen had an objective response rate of 33% in the letrozole arm (n=369) vs. 24% in the tamoxifen arm (n=371), P=0.0039. In patients who had received prior

adjuvant tamoxifen, significantly more patients achieved an objective response rate with letrozole (26%) vs. tamoxifen (8%), P=0.0038. These data demonstrate that the Objective Response Rate with FEMARA is superior to tamoxifen regardless of whether prior adjuvant therapy was initiated.

FEMARA treatment in first-line therapy of advanced breast cancer patients is associated with an early survival advantage over tamoxifen. The median overall survival was 34 months for FEMARA and 30 months for tamoxifen. Although this difference in overall survival was not statistically significant (logrank P=0.53), there was a statistically significant early survival advantage for patients in the randomized FEMARA arm compared to the randomized tamoxifen arm over the first 2 years, as shown in the primary analysis (Kolmogorov-Smirnov-type test, P=0.005). Supportive analyses (repeated logrank tests) confirmed the early survival advantage (see Figure 6). The total duration of endocrine therapy (time to chemotherapy) was significantly longer for FEMARA (median 16 months, 95% CI 15 to 18 months) than for tamoxifen [(median 9 months, 95% CI 8 to 12 months) (logrank P=0.0047)].

Figure 6



Second-Line Treatment

In a controlled double-blind clinical trial, the overall objective tumour response rate (complete and partial response) was 23.6% in FEMARA-treated patients compared to 16.4% in patients on 160 mg megestrol acetate. Treatment comparison of the response rate showed a statistically significant difference in favour of 2.5 mg FEMARA (p=0.04).

In an open-label, randomized clinical trial, survival at 2 years was 55.1% for patients treated with FEMARA compared to 38.8% for patients treated with 500 mg aminoglutethimide. Treatment comparison showed a statistically significantly prolonged overall survival with FEMARA (adjusted Cox regression hazard ratio 0.68, 95% CI 0.52-0.87, p=0.003).

DETAILED PHARMACOLOGY

Animal Pharmacology

Pharmacodynamics

Letrozole is a more potent and selective aromatase inhibitor than aminoglutethimide (AG). *In vitro* studies in human placental microsomal preparations showed that letrozole is about 150-250 times more potent than AG in its aromatase inhibition. This selectivity was documented by studying inhibition of estradiol and progesterone synthesis in hamster ovarian slices *in vitro*, and inhibition of adrenal steroidogenesis in rat adrenal fragments *in vitro* (see Table 13).

Table 13 Inhibition of steroid production *in vitro*

	AG	letrozole	anastrozole	formestane
IC_{50} nM *(Rel. Potency)**	1900 *(1)*	11.5 *(165)*	15 *(127)*	62 *(31)*
K_i nM *(Rel. Potency)*	530 *(1)*	2.1 *(250)*	-	20 *(26.5)*

* Concentration required to inhibit steroid production by 50%.

The results show that, when compared with the IC_{50} for estradiol production, letrozole does not inhibit corticosterone production at concentrations 17,000 times higher and inhibits aldosterone production at concentrations 10,000 times higher than those required for inhibiting estrogen production. In contrast, AG inhibits estradiol, corticosterone and aldosterone at concentrations which are within one order of magnitude of each other.

Letrozole is >650 times more potent than AG in inhibiting estradiol production, whereas formestane is about 30 times more potent, and anastrozole, about 127 times more potent. Further, whereas AG inhibited adrenal steroidogenesis (corticosterone and aldosterone), letrozole did not, even at concentrations 3 orders of magnitude higher than those required for inhibition of estradiol production.

To complement the *in vitro* studies in rat adrenal fragments, inhibition of adrenal steroidogenesis was investigated in ACTH-stimulated male rats *in vivo*. At 4 mg/kg p.o., letrozole showed no

significant effect on plasma concentrations of either corticosterone or aldosterone in ACTH-stimulated male rats. This dose is about 500 times higher than the dose which was maximally effective in inhibiting aromatase *in vivo* and 4 times higher than the dose which was as effective as ovariectomy in reducing uterine weight in adult female rats. Under the same experimental conditions, AG at a dose of 100 mg/kg p.o. significantly suppressed plasma concentrations of both corticosterone and aldosterone.

Aromatase-mediated uterine hypertrophy was antagonized by letrozole with an ED_{50} of 1-3 µg/kg and a minimum effective dose of 0.3 µg/kg when administered orally to pre-pubertal rats treated with androstenedione. AG, under the same conditions, antagonized this androstenedione-induced uterotrophic effect with an ED_{50} of 30 mg/kg. Thus, in this assay, letrozole is over 10,000 times as potent as AG.

In adult female rats treated for 14 days with 0.03, 0.1, and 1 mg/kg letrozole p.o., there was a dose-dependent increase in body weight and LH, in addition to a highly pronounced, significant, dose-dependent effect on the disruption of ovarian cyclicity (all rats in continuous diestrus at 1 mg/kg) and reduction of relative uterine weight. At 1 mg/kg, letrozole was as effective as ovariectomy in causing these estrogen-related changes.

In a study comparing the effects of a 14-day treatment with letrozole and anastrozole on the uterus in adult cyclic rats, 1 mg/kg letrozole was again shown to be equivalent to ovariectomy in reducing uterine weight. Anastrozole, in contrast, at doses of 1 and 10 mg/kg, did not significantly affect uterine weight when compared to a group of untreated control animals. Thus, letrozole is more than 10 times as potent as anastrozole in reducing uterine weight.

In estrogen-dependent DMBA- and NMU-induced mammary carcinomas in adult female rats, oral daily treatment with letrozole for 6 weeks resulted in a dose-dependent effect on mean tumour volume with an estimated ED_{50} of 0.03 mg/kg. Maximal efficacy was seen in both models at 0.3 mg/kg. At this dose, letrozole suppressed appearance of new tumours.

In a direct comparison between letrozole (0.1-1 mg/kg) and anastrozole (1-10 mg/kg) in rats bearing DMBA-induced mammary carcinomas, 0.1 mg/kg letrozole was more effective in reducing mean tumour volume than was anastrozole at a dose of 10 mg/kg. Thus in this DMA model, the anti-tumour efficacy of letrozole is more than 100-fold higher than that of anastrozole.

In a 104-week carcinogenicity study in rats there was a dose-dependent decrease in the incidence of benign and malignant spontaneous mammary tumours in females at all doses (0-10 mg/kg) compared to controls. At the highest dose, appearance of spontaneous benign or malignant tumours was completely suppressed.

Pharmacokinetics

Peroral absorption of single doses of letrozole was almost complete in all species studied (mice, rats, dogs). Peroral bioavailability was high in all three species, indicative of low first-pass metabolism.

In mice, rats and dogs, unchanged letrozole was the predominant drug-related substance in the plasma. In all three species, systemic exposure to letrozole metabolites was at most very low, thus, following administration of ^{14}C-letrozole the concentrations of total radioactivity in plasma approximate those of unchanged letrozole.

Clearance of the parent drug from plasma decreased in the order: mouse > male rat > female rat > dog. After single doses, the apparent terminal plasma elimination half-life was approximately 4-5 hours in mice, 7-10 hours in male rats, 20-50 hours in female rats and 60-90 hours in dogs. Dose- and time-dependent kinetics were observed in rats.

Radioactivity from ^{14}C letrozole was distributed rapidly and extensively throughout the whole body of mice, rats and dogs. Particularly high levels were seen in the adrenals and liver. In pigmented rats, letrozole showed a marked but reversible affinity for melanin-containing structures of the eye and fur. Radioactivity declined substantially in the 14 days after dosing followed by a very slow terminal decline of low residual radioactivity levels.

Similar metabolic profiles between species (including humans) and genders suggest that the same pathways are involved, but that differences in the quantity of enzymes and in the renal clearance of letrozole affect the rate and extent of metabolism. Metabolic clearance, mainly formation of the carbinol metabolite, CGP 44645, followed by glucuronidation, is the major clearance pathway in rats and man. In mice, renal excretion of unchanged letrozole is the major elimination pathway.

Human Pharmacodynamics

Adjuvant and extended adjuvant setting

Updated results from the extended adjuvant study bone substudy (median follow-up of 61 months) indicated a significantly greater decrease in BMD from baseline for hip BMD at 24 months (Table 14).

Table 14 **Percentage change from baseline in bone mineral density (BMD) of total hip and lumbar spine in extended adjuvant bone substudy (Per protocol bone substudy population)**

MA-17 bone substudy		Lumbar spine (L2-L4)[1]		Total hip[2]	
Month	Statistic	**FEMARA**	**Placebo[3]**	**FEMARA**	**Placebo[3]**
12	N	99	87	98	88
	Median	-2.4	-2.4	-2.2	-2.3
24	N	94	44	94	45
	Median	-3.7	-2.0	-3.8[4]	-2.0
36	N	81	12	80	11
	Median	-2.9	-0.4	-3.7	-1.7
48	N	78	2	76	2
	Median	-2.8	-4.0	-4.2	-5.0
60	N	73	2	71	2
	Median	-3.0	-5.3	-3.6	-6.7

[1] Primary endpoint in bone substudy
[2] Secondary endpoint
[3] Placebo until switch (if a switch occurred)
[4] Statistically significant difference from placebo on Wilcoxon signed rank test (adjusted for bisphosphonate use)
Note: All patients should have received vitamin D and calcium supplementation. Vitamin D was not recorded. Calcium supplementation was reported for 44-66% of patients. Bisphosphonates were received by approximately a third of the patients treated with FEMARA, compared with a quarter or fewer patients in the placebo arm.

Table 15 summarizes clinically relevant changes in study D2407 after adjuvant treatment with FEMARA or tamoxifen for 2 years.

Table 15 **Clinically relevant changes in lumbar spine and total hip BMD in adjuvant study after 2 years treatment (Per protocol population)**

D2407 study	Lumbar spine (L2-L4)		Total hip	
	FEMARA	**Tamoxifen**	**FEMARA**	**Tamoxifen**
Clinically relevant change from baseline	**N=103 n (%)**	**N=97 n (%)**	**N=103 n (%)**	**N=97 n (%)**
No. of pts with ≥ 1 change	34 (33.0)	22 (22.7)	25 (24.3)	25 (25.8)
6% reduction in 1 year	21 (20.4)	2 (2.1)	9 (8.7)	4 (4.1)
8% cumulative reduction	16 (15.5)	1 (1.0)	8 (7.8)	3 (3.1)
T-score -2.5 or lower	1 (1.0)	-	-	-
Clinical fracture	4 (3.9)	6 (6.2)	4 (3.9)	6 (6.2)
Impending fracture	11 (10.7)	15 (15.5)	11 (10.7)	15 (15.5)

There was no significant difference between treatments in the number of patients who had 1 or more clinically relevant change in BMD over 2 years (odds ratio).

Table 15 Clinically relevant changes in lumbar spine and total hip BMD in adjuvant study after 2 years treatment (Per protocol population)

D2407 study	Lumbar spine (L2-L4)		Total hip	
	FEMARA	Tamoxifen	FEMARA	Tamoxifen
Clinically relevant change from baseline	N=103 n (%)	N=97 n (%)	N=103 n (%)	N=97 n (%)

Note: All patients should have received vitamin D and calcium supplementation. Post baseline bisphosphonates were given in 14% of patients treated with FEMARA, 5% of those treated with tamoxifen.

Table 16 summarizes clinically relevant changes in study D2407 after adjuvant treatment with FEMARA at 5 years

Table 16 Clinically relevant changes in lumbar spine (L2-L4) and total hip BMD at 5 years by central assessment (Safety population)

	FEMARA	
	Lumbar spine N=133 n (%)	Total hip N=130 n (%)
Number of patients with one or more of following changes:	68 (51.1)	60 (45.1)
6% reduction over a year	32 (24.1)	14 (10.5)
8% reduction at any time up to 5 years	33 (24.8)	26 (19.5)
T-score ≤ -2.5 at any time up to 5 years [1]	9 (6.8)	
Fracture at or before 5 years [2]	17 (12.8)	
Impending fracture at or before 5 years [3]	19 (14.3)	

[1] Based on DXA readings centrally assessed, all 9 patients had either a lumbar spine or a total hip T-score below -2.5 at baseline.

[2] Clinical fractures evaluated centrally on DXA scans and/or on X-ray. Clinical fractures include fractures at any site.

[3] Impending fractures evaluated centrally only, seen on X-ray.

Table 17 summarizes updated results from the extended adjuvant lipid substudy (median follow-up of 62 months). There were no significant differences between FEMARA and placebo in changes from baseline in total cholesterol or any lipid fraction.

Table 17 Percentage change in total cholesterol and LDL cholesterol in the extended adjuvant lipid substudy (Per protocol lipid population)

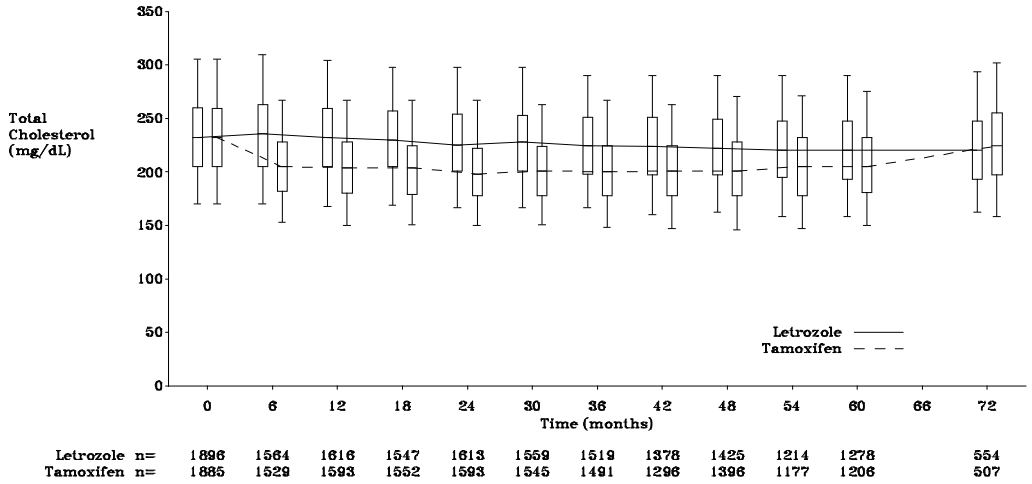
MA-17 lipid substudy		Total cholesterol		LDL cholesterol	
Month	**Statistic**	**FEMARA**	**Placebo[1]**	**FEMARA**	**Placebo[1]**
6	N	140	115	140	114
	Median	13.70	11.79	21.31	21.28
12	N	137	114	136	113
	Median	16.81	11.71	28.14	23.13
24	N	128	84	128	84
	Median	14.40	12.18	22.11	24.94
36	N	120	50	120	49
	Median	9.69	11.06	19.18	21.60
48	N	12	19	102	19
	Median	6.16	7.92	13.02	12.21
60	N	85	8	85	8
	Median	9.29	11.40	15.74	9.93

[1] Placebo until switch (if switch occurred)

In the adjuvant study, D2407, although total cholesterol and LDL cholesterol values remained stable over 2 years in the FEMARA arm, a median decrease of around 16% in total cholesterol and around 20% in LDL cholesterol was observed at 6 months in the tamoxifen arm, with subsequent values remaining around the same decreased levels, leading to significant differences between treatments at all time-points in total cholesterol, LDL cholesterol and the HDL:LDL ratio. No significant treatment differences were observed over the 2 years in triglyceride levels.

In the large adjuvant study BIG 1-98, total cholesterol levels (generally measured under non-fasting conditions) remained stable over 5 years of treatment in the FEMARA arm. In the tamoxifen arm, there was an immediate decrease of around 14% observed at 6 months with subsequent median decreases of 10-14% over 5 years of treatment, returning to baseline levels 1 year after treatment completion (Figure **7**).

Figure 7 Total cholesterol values over time in adjuvant study, BIG 1-98 (Safety population)



Overall, in the large adjuvant study BIG 1-98, there was a significantly higher risk of hypercholesterolemia for FEMARA relative to tamoxifen (RR 1.83; 95% CI 1.70, 1.97), albeit at low CTC grades (0.4% of patients receiving FEMARA had CTC grade 3-4 hypercholesterolemia). Lipid-lowering agents were given post baseline in approximately 25 % of patients treated with FEMARA, compared with approximately 16% treated with tamoxifen.

TOXICOLOGY

In a variety of preclinical safety studies conducted in standard animal species, there was no evidence of systemic or target organ toxicity.

Letrozole showed a low degree of acute toxicity in rodents exposed up to 2000 mg/kg. In dogs, letrozole caused signs of moderate toxicity at 100 mg/kg (see Table 18).

In repeated dose toxicity studies of up to 12 months duration in rats treated with 0.3, 3 and 30 mg/kg and dogs treated with 0.03, 0.3 and 3 mg/kg, the main findings can be attributed to the pharmacological action of the compound. Effects on the liver (increased weight, hepatocellular hypertrophy, fatty changes) were observed, mainly at the high dose level. The no-adverse effect level was 0.3 mg/kg in both species (see Table 19). Increased incidences of hepatic vacuolation (both sexes, high dose) and necrosis (intermediate and high dose females) were also noted in rats treated for 104 weeks in a carcinogenicity study. They may have been associated with the endocrine effects and hepatic enzyme-inducing properties of FEMARA. However, a direct drug effect cannot be ruled out.

The pharmacological effects of letrozole resulted in skeletal, neuroendocrine and reproductive findings in a juvenile rat study at doses between 0.003 mg/kg/day and 0.3 mg/kg/day. Bone

growth and maturation were decreased from the lowest dose (0.003 mg/kg/day) in males and increased from the lowest dose (0.003 mg/kg) in females. Bone mineral density (BMD) was also decreased at that dose in females. In the same study, decreased fertility at all doses was accompanied by hypertrophy of the hypophysis, testicular changes which included a degeneration of the seminiferous tubular epithelium, ovarian edema, ovarian cysts and atrophy of the female reproductive tract. Effects on bone size in females at 0.3 mg/kg/day and males at 0.03 mg/kg/day and morphological changes in the testes were not reversible. All other effects were at least partially reversible at 0.003 mg/kg/day and 0.03 mg/kg/day.

Table 18 Acute Toxicity

Species	Dose mg/kg	Route	Findings
Mouse	200, 2000	p.o.	LD_{50}: >2000 mg/kg
Rat	2000	p.o.	LD_{50}: >2000 mg/kg
Dog	100, 200	p.o.	100 mg/kg: signs of general toxicity; 12 days after dosing: asymptomatic. 200 mg/kg: death within 48 hours
Rat	50, 500	i.p.	LD_{50}: >500 mg/kg

Table 19 Long-Term Toxicity

Duration of dosing	Species	Dose (mg/kg) /Route	Main findings
13 weeks	Mouse	0.6, 6, 60 /p.o.	Pharmacological effects on reproductive tract. 60 mg/kg: ↑ Liver weight
28 days (pilot)	Rat	0.5, 5, 50 /p.o.	Pharmacological effects on reproductive tract. 50 mg/kg: ↑ Liver weight
3 months	Rat	0.3, 3, 30 /p.o.	Pharmacological effects on reproductive tract. 3 and 30 mg/kg: ↑ Liver weight 30 mg/kg: Signs of thyroid activation. **No-adverse effect level: 0.3 mg/kg.**
6/12 months	Rat	0.3, 3, 30 /p.o.	Pharmacological effects on reproductive tract. 30 mg/kg: Fractures of long bones (5/40 f); liver weight ↑ (m). **No-adverse effect level: 0.3 mg/kg.**

Table 19 Long-Term Toxicity

Duration of dosing	Species	Dose (mg/kg) /Route	Main findings
12 weeks (from day 7 post partum) + 6 weeks recovery	Rat	0.003, 0.03 and 0.3 mg/kg/day. Oral gavage	Bone growth and maturation ↓ from 0.003 in males and ↑ from 0.003 in females BMD ↓ 0.003 in females From 0.003, ↓fertility, hypertrophy of the hypophysis, testicular changes which included a degeneration of the seminiferous tubular epithelium and ovarian edema From 0.03, ovarian cysts and atrophy of the female reproductive tract
28 days (pilot)	Dog	5 /p.o.	Pharmacological effects on reproductive tract.
3 months	Dog	0.03, 0.3, 3.0 /p.o.	Pharmacological effects on reproductive tract. Hypertrophy Leydig cells, impaired spermatogenesis at 0.03 mg/kg.
6/12 months	Dog	0.03, 0.3, 3.0 /p.o.	Pharmacological effects on reproductive tract. 3 mg/kg: Centrilobular hypertrophy of liver cells (f). **No-adverse effect level: 0.3 mg/kg**

Two 104-week carcinogenicity studies have been conducted. In one study, rats were treated with letrozole, administered orally, in doses of 0.1, 1.0 and 10 mg/kg/day; in the second study, mice were treated with letrozole orally at doses of 0.6, 6 and 60 mg/kg/day. No treatment related tumours were noted in male animals. In female animals, treatment related changes in genital tract tumours (a reduced incidence of benign and malignant mammary tumours at all doses in rats and an increased incidence of benign ovarian granulosa theca cell tumours at all doses in mice) were secondary to the pharmacological effect of the compound. In the mouse carcinogenicity study, dermal and systemic inflammations were also noted, particularly in the high dose group, leading to increased mortality at this dose level. It is not known whether these findings were an indirect consequence of the pharmacological activity of letrozole (i.e. linked to long-term estrogen deprivation) or a direct drug effect.

Table 20 Mutagenicity Studies

Study	Test System(s)	Strain(s)/ Target cells	Concentration / Dose	Observations
in vitro				
Ames	Salmonella typhimurium	TA 98, 100, 1535, 1537	313-5000 µg/plate*	No evidence of mutagenicity

Study	Test System(s)	Strain(s)/ Target cells	Concentration / Dose	Observations
gene mutation	Chinese Hamster cells	V 79 cells	60-1800 µg/mL*	No evidence of mutagenicity
chromosome aberration	Chinese Hamster cells	Ovary cell line CCL 61	Chromosome study: 50/800 µg/mL* Cytogenetic test: 145-1160 µg/mL*	No mutagenic or clastogenic effects
in vivo				
Micronucleus	Rat		40, 80, 160 mg/kg / p.o.	No clastogenic or aneugenic effects

* With or without metabolic activation by a fraction of rat liver microsomes (S-9 mix)

Reproductive and Development Toxicology:
Letrozole was evaluated for maternal toxicity as well as embryotoxic, fetotoxic and teratogenic potential in female rats and rabbits. Oral administration of letrozole to pregnant Sprague-Dawley rats resulted in teratogenicity and maternal toxicity at 0.03 mg/kg (about 1/10 the daily maximum recommended human dose (MRHD)), and embryotoxicity and fetotoxicity at doses ≥0.003 mg/kg (about 1/100 the daily MRHD). Teratogenic effects included fetal domed head and cervical/centrum vertebral fusion. Embryotoxic and fetotoxic effects included 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. In New Zealand White rabbits, letrozole was embryotoxic at doses ≥ 0.002 mg/kg, and fetotoxic when administered at 0.02 mg/kg (about 1/100,000 and 1/10,000 the daily MRHD). Fetal anomalies included incomplete ossification of the skull, sternebrae, and forelegs and hind legs. It is not known whether these effects are an indirect consequence of the pharmacological activity of FEMARA (inhibition of estrogen biosynthesis) or a direct drug effect.

Oral administration of letrozole to female rats resulted in a decrease in mating ratio at 0.03 mg/kg. No animals mated at 0.3 mg/kg. Decreases in pregnancy ratios were noted at doses as low as 0.003 mg/kg and increases in pre-implantation loss at doses of 0.003 and 0.03 mg/kg.

Oral administration of letrozole to male rats at doses of 0, 0.03, 0.3 or 3 mg/kg/day resulted in adverse effects on male fertility at all doses, and included alterations in sperm parameters (decreased counts and motility) as well as testicular changes (decreased weights, pallor, tubular atrophy). Secondary to these effects, severe reductions in the number of sperm-positive and pregnant females were evident in all treatment groups.

Exposure of lactating rats to letrozole was associated with an impaired reproductive performance of the male offspring at a letrozole dose as low as 0.003 mg/kg/day. There were no effects on the reproductive performance of female offspring.

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CONSUMER INFORMATION

[Pr]FEMARA®
(letrozole tablets)

This leaflet is part III of a three-part "Product Monograph" published when FEMARA® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about FEMARA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What FEMARA is used for:

- The adjuvant treatment of postmenopausal women with hormone receptor-positive invasive early breast cancer;
- The extended adjuvant treatment of hormone receptor positive invasive early breast cancer in postmenopausal women who have received approximately 5 years of prior standard adjuvant tamoxifen therapy;
- The first-line therapy in postmenopausal women with advanced breast cancer; and
- The hormonal treatment of advanced metastatic breast cancer after relapse or disease progression in women with natural or artificially-induced postmenopausal endocrine status, who have previously been treated with antiestrogens.

What does FEMARA do:

Estrogen is a normally occurring female sex hormone that stimulates normal breast tissue and the growth of some types of breast cancer. FEMARA is an aromatase inhibitor which acts by binding to aromatase, a substance needed to make estrogen. As a result, the production of estrogen and the growth of breast cancer are reduced.

What is adjuvant therapy:
Adjuvant therapy in breast cancer refers to treatment following breast surgery (the primary or initial treatment) in order to reduce the risk of recurrence. The purpose of adjuvant therapy with FEMARA is to treat hormone receptor-positive early breast cancer, after surgery, in postmenopausal women to reduce the risk of recurrence.

What is extended adjuvant therapy:
The purpose of extended adjuvant therapy with FEMARA is to treat hormone receptor-positive early breast cancer in postmenopausal women who have received approximately 5 years of prior standard adjuvant tamoxifen therapy in order to prevent recurrence. Treating breast cancer with FEMARA beyond the standard 5 years of hormone therapy is called "extended adjuvant therapy".

When it should not be used:

FEMARA should not be used in children and adolescents under 18 years of age.

FEMARA should not be used in hormone-receptor negative disease.

Do not take FEMARA if you:
- have ever had an unusual or allergic reaction to letrozole or any other ingredient in FEMARA;
- still have menstrual periods;
- are pregnant or breast-feeding, as FEMARA may harm your baby.

What the medicinal ingredient is:

Letrozole

What the nonmedicinal ingredients are:

FEMARA also contains the following non-medicinal ingredients needed to make the tablets: cellulose compounds (microcrystalline cellulose and methylhydroxypropylcellulose), corn starch, iron oxide, lactose, magnesium stearate, polyethylene glycol, sodium starch glycolate, silicon dioxide, talc and titanium dioxide.

What dosage forms it comes in:

FEMARA (letrozole) 2.5 mg tablets

FEMARA is supplied as film-coated tablets. The film-coated tablets are dark-yellow and round with bevelled edges. They are marked with "FV" on one side and "CG" on the other.

FEMARA is supplied in blister packs containing 30 tablets.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

FEMARA should be used under the supervision of a doctor experienced in the use of anti-cancer drugs.

FEMARA reduces blood estrogen levels which may cause a reduction in bone mineral density and a potential increase in bone loss (osteoporosis) and/or bone fractures.

The use of aromatase inhibitors, including FEMARA, may increase the risk of cardiovascular events compared to tamoxifen, such as heart attacks and stroke. Women at risk of heart disease should be carefully monitored by their doctor.

You should **not** use FEMARA if you may become pregnant, or are pregnant. There is a potential risk of harm to you and the fetus. There are reports of spontaneous abortions and abnormalities in babies born to mothers who took FEMARA during pregnancy. If you have the potential to become pregnant (this includes women who are perimenopausal or who recently became postmenopausal), you should discuss with your doctor about the need for effective contraception. Use effective birth control during treatment and for at least 20 days after stopping

FEMARA. Ask your doctor about options of for effective birth control.

You should **not** use FEMARA if you are breastfeeding. There is a potential risk of harm to breastfed babies.

Femara may reduce fertility in males.

If there is exposure to FEMARA during pregnancy, you should contact your doctor immediately to discuss the potential of harm to your fetus and potential risk for loss of the pregnancy.

FEMARA should not be used in children and adolescents under 18 years of age.

Before you take FEMARA:

Tell your doctor if you:

- have a serious kidney or serious liver disease;
- are taking hormone replacement therapy;
- are taking other medication to treat your cancer;
- have a personal or family history of osteoporosis or have ever been diagnosed with low bone density or have a recent history of fractures (in order for your doctor to assess your bone health on a regular basis);
- have a personal or family history of high blood cholesterol or lipid levels. FEMARA may increase lipid levels;
- have or have had cardiovascular or heart disease including any of the following: heart attack, stroke or uncontrolled blood pressure. FEMARA may increase the risk of cardiovascular or heart diseases;
- have an intolerance to milk sugar (lactose);
- have pain in bones, or joints or muscles.

Your level of hormones may be checked by your doctor before you take FEMARA and regularly during the first 6 months of treatment to confirm your menopausal status (cessation of periods).

Driving a vehicle or using machinery:

FEMARA tablets are unlikely to affect your ability to drive a car or to use machinery. However, some patients may occasionally feel tired, dizzy, sleepy or experience visual disorders. If this happens, you should not drive or operate any tools or machinery until you feel normal again.

INTERACTIONS WITH THIS MEDICATION

Please tell your doctor or pharmacist if you are taking or have recently taken any other prescription or over-the-counter medicines, vitamins or natural health products during your treatment with FEMARA. This includes in particular:

- Tamoxifen.
- Other anti-estrogens or estrogen-containing therapies.

These substances may diminish the action of FEMARA.

PROPER USE OF THIS MEDICATION

Usual dose:

The usual dosage is one tablet of FEMARA to be taken once daily. The tablet should be swallowed whole with a small glass of water. You can take FEMARA with or without food. It is best to take FEMARA at about the same time every day.

Overdose:

If overdosage is known or suspected, contact your doctor or the nearest poison control centre for advice immediately. Show the pack of tablets. Medical treatment may be necessary.

Missed Dose:

If you forget to take a dose of FEMARA, don't worry, take the missed dose as soon as you remember. However, if it is almost time for the next dose (e.g. within 2 or 3 hours), skip the missed dose and go back to your regular dosage schedule. Do not take a double dose to make up for the one that you missed.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with all medicines, patients taking FEMARA may experience side effects. Most side effects that have been observed were mild to moderate and will generally disappear after a few days to a few weeks of treatment. Check with your doctor if the unwanted effects do not go away during treatment or become bothersome.

Some side effects, such as hot flushes, hair loss or vaginal bleeding may be due to the lack of estrogen in your body.

Very common side effects (*they affect more than 10 in every 100 patients*)

- increased level of cholesterol (hypercholesterolemia)
- hot flushes
- increased sweating
- night sweats
- fatigue (including weakness and malaise (generally feeling unwell))
- pain in bones and joints (arthralgia).

Common side effects (*they affect between 1 to 10 in every 100 patients*)

- headache
- rash
- dizziness, vertigo
- gastrointestinal disorders (such as, nausea, vomiting, indigestion, constipation, diarrhea)
- increase in or loss of appetite
- increased blood sugar (hyperglycaemia)
- urinary incontinence
- pain in muscles
- bone loss (osteoporosis)
- bone fractures
- depression
- weight increase
- anxiety
- insomnia
- hair loss

- vaginal bleeding
- dry skin
- raised blood pressure (hypertension)
- abdominal pain.
- Back pain
- Fall
- Palpitations (rapid heart rate)
- Joint stiffness (arthritis)
- Chest pain

Uncommon side effects (*they affect between 1 to 10 in every 1000 patients*)

- nervous disorders (such as nervousness, irritability, drowsiness)
- pain or burning sensation in the hands or wrists (carpal tunnel syndrome)
- reduced sense of touch (dysaesthesia)
- eye irritation
- itchy rash (urticaria), rapid swelling of face, lips, tongue, throat (angioedema)
- severe allergic reaction (anaphylactic reaction)
- vaginal disorders (such as discharge or dryness)
- breast pain
- fever
- thirst, taste disorder, dry mouth
- dryness of mucous membranes
- weight decrease
- urinary tract infection, increased frequency of urination
- cough
- abnormal liver function test results (blood test disorders)
- Increased bilirubin level (dark coloured urine)
- Jaundice (yellowish eyes and/or skin).

Side effects with frequency not known

- trigger finger, a condition in which your finger or thumb catches in a bent position.

If any of these affects you severely, **tell your doctor**.

If you notice any other side effects not listed in this leaflet, please tell your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Common			
-Pain in the muscles, bones and joints;	√		
-Joint stiffness;	√		
-Persistent sad mood (i.e. depression).		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Uncommon			
- Tightness or feeling of heaviness in the chest or pain radiating from your chest to your arms or shoulders, neck, teeth or jaw, abdomen or back (signs of angina pectoris or heart attack);			√
umbness or weakness in arm or leg or any part of the body, loss of coordination, vision changes, sudden headache, nausea, loss of coordination, difficulty in speaking or breathing (signs of brain disease e.g. stroke);			√
- Swelling and redness along a vein which is extremely tender and possibly painful when touched (signs of inflammation of a vein due to a blood clot, e.g. thrombophlebitis);			√
- Difficulty breathing, chest pain, fainting rapid heart rate, bluish skin discoloration (signs of blood clot formation in the lung such as pulmonary embolism);			√
- Swelling of arms, hands, feet, ankles or other parts of the body (signs of oedema);			√
- Swelling mainly of the face and throat (signs of allergic reaction);			√
- Severe fever, chills or mouth ulcers due to infections (signs of low level of white blood cells);			√
- Blurred vision (sign of cataract);			√
- Yellow skin and eyes, nausea, loss of appetite, dark-coloured urine (signs of hepatitis);			√
ash, red skin, blistering of the lips, eyes or mouth, skin peeling, fever (signs of skin disorder).			√

This is not a complete list of side effects. For any unexpected effects while taking FEMARA, contact your doctor or pharmacist.

HOW TO STORE IT

Store your tablets in a dry place at room temperature 15 to 30 °C. Avoid places where the temperature may rise above 30°C.

Protect from moisture.

Keep this medicine out of the reach and sight of children and pets.

Expiry date:

Do not take FEMARA after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of the month. Remember to take any unused medication back to your pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701E
  Ottawa, Ontario
  K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
www.novartis.ca

or by contacting the sponsor, Novartis Pharmaceuticals Canada Inc, at:
1-800-363-8883

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