PRODUCT MONOGRAPH

[Pr]LETROZOLE

(letrozole)

Letrozole tablets, USP

2.5 mg

Non-steroidal aromatase inhibitor; inhibitor of estrogen biosynthesis; antitumour agent

LETROZOLE (letrozole) indicated for:

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

has been issued market authorization with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the market authorization granted.

LETROZOLE, indicated for:

- The first-line therapy in postmenopausal women with advanced breast cancer;
- The hormonal treatment of advanced/metastatic breast cancer in women with natural or artificially-induced postmenopausal status, who have disease progression following antiestrogen therapy;

has been issued market authorisation without conditions.

LETROZOLE should be administered under the supervision of a qualified physician experienced in the use of anti-cancer agents.

Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
M1B 2K9

Date of Revision:
February 10, 2010

Submission Control No: 137039

This product has been approved under the Notice of Compliance with Conditions (NOC/c) policy for one or all of its indicated uses.

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products approved under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

What will be different about this Product Monograph?

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol NOC/c. These sections may include, but are not limited to, the following:

- Indications and Clinical Uses;
- Action;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

Adverse Drug Reaction Reporting and Re-Issuance of the Product Monograph

Health care providers are encouraged to report Adverse Drug Reactions associated with normal use of these and all drug products to Health Canada's Health Product Safety Information Division at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

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(letrozole)

Letrozole tablets, USP
2.5 mg

PART I: HEALTH PROFESSIONAL INFORMATION

LETROZOLE (letrozole), indicated for:

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

has been issued market authorization with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the market authorization granted.

LETROZOLE, indicated for:

- The first-line therapy in postmenopausal women with advanced breast cancer;
- The hormonal treatment of advanced/metastatic breast cancer in women with natural or artificially-induced postmenopausal status, who have disease progression following antiestrogen therapy;

has been issued market authorisation without conditions.

LETROZOLE should be administered under the supervision of a qualified physician experienced in the use of anti-cancer agents.

SUMMARY PRODUCT INFORMATION

Route of Administration	**Dosage Form / Strength**	**Clinically Relevant Non-medicinal Ingredients**
Oral	Tablets, 2.5 mg	*For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

INDICATIONS AND CLINICAL USE

NOC/c LETROZOLE (letrozole) is indicated for the adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer.

Approval is based on superior Disease-Free Survival (DFS) compared to tamoxifen from the overall study population, at a median follow-up of 26 months. However, DFS advantage of letrozole over tamoxifen was not observed in the subset of patients with node-negative disease (see **CLINICAL TRIALS** section).

NOC/c LETROZOLE (letrozole) is also indicated for the extended adjuvant treatment of hormone receptor-positive early breast cancer in postmenopausal women who have received approximately 5 years of prior standard adjuvant tamoxifen therapy.

Although the intended duration of extended adjuvant therapy with letrozole is 5 years, randomized, double-blinded data on efficacy endpoints is limited to a median follow-up of 28 months. After this time, the study was unblinded and patients who had received placebo had the option to switch in a non-randomized fashion to treatment with letrozole. At a median follow-up of 30 months, a non-significant increase in deaths (P=0.749) occurred in the letrozole arm in node-negative patients (HR 1.1 (CI 0.62, 1.96): 24/1298 in the letrozole arm versus 22/1301 in the placebo arm). The clinical evidence collected to date demonstrates a statistically significant increase in disease-free survival, but no overall survival advantage has been consistently demonstrated.

NOC LETROZOLE (letrozole) is indicated as first-line therapy in postmenopausal women with advanced breast cancer.

NOC LETROZOLE (letrozole) is also indicated for the hormonal treatment of advanced/metastatic breast cancer in women with natural or artificially-induced postmenopausal status, who have disease progression following antiestrogen therapy.

CONTRAINDICATIONS

- Premenopausal endocrine status, pregnancy, lactation (see **WARNINGS AND PRECAUTIONS** section).

- 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 of the product monograph.

- In the absence of clinical experience with the use of letrozole in children or adolescents (under 18 years of age), LETROZOLE should not be used in these patients.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

LETROZOLE (letrozole) should be administered under supervision of a qualified physician experienced in the use of anti-cancer agents.

- Osteoporosis (see Musculoskeletal section, below).

General

Clinical trial evidence (median follow-up duration of 26 months in the adjuvant setting, 49 months in the extended adjuvant setting) is insufficient to assess adverse effects associated with long term use of letrozole for five years.

Ability to drive and use machines: Since fatigue and dizziness have been observed with the use of letrozole, and somnolence has been reported uncommonly, caution is advised when driving or using machines.

Cardiovascular Disease

In the adjuvant setting, the use of some aromatase inhibitors, including LETROZOLE, may increase the risk of cardiovascular events compared to tamoxifen. The overall incidence of cardiovascular events in the BIG 1-98 study for letrozole and tamoxifen arms was 9.7 vs. 10.5%, respectively. However, a higher incidence of events was seen for letrozole vs. tamoxifen, including cardiac failure (0.9 vs. 0.4%, respectively), myocardial infarction (0.8 vs. 0.4%, respectively), fatal cardiac events (0.6 vs. 0.3%, respectively) and numerically higher fatal stroke (0.15%, 6 cases vs. 0.03%, 1 case, respectively), and a lower incidence was seen for thromboembolic events (1.4% vs. 3.0%, respectively). Patients with non-malignant systemic diseases (cardiovascular, renal, hepatic, lung embolism etc.) which would prevent prolonged follow-up were ineligible from enrolment in the BIG 1-98 trial (see **Clinical Trial Adverse Drug Reactions** section).

In the extended adjuvant setting, in a 5-year, phase III trial, after a median follow-up of 28 months, the incidence of cardiovascular events any time after randomization was comparable between treatment arms; 6.8% in the letrozole arm compared to 6.5% in the placebo arm. The most frequent cardiovascular events were: new or worsening angina (1.4% in the letrozole arm vs. 1.0% in the placebo arm), myocardial infarction (0.6% in the letrozole arm vs. 0.7% in the placebo arm), and stroke/transient ischemic attack (0.9% in the letrozole arm vs. 0.9% in the placebo arm). These results were obtained prior to unblinding the study.

After the study unblinding, patients randomized to the placebo arm were offered to switch to letrozole or discontinue treatment.

The updated results obtained from this Phase III study after study unblinding showed that after a median follow-up of approximately 49 months, the frequency of cardiovascular events any time

after randomization was higher in the letrozole arm than in placebo arm until the switch (11.1% vs. 8.6%, respectively). The most frequent cardiovascular events included arrhythmia (4.0% in the letrozole arm vs. 3.3% in the placebo arm until switch), new or worsening angina (1.7% on letrozole vs. 1.2% on placebo until switch), and stroke/transient ischemic attack (1.7% on letrozole vs. 1.3% on placebo until the switch).

At a median follow-up of approximately 49 months, the number of deaths attributed to a cardiovascular cause during treatment or within 30 days of stopping treatment was slightly higher in the placebo arm [16/2577 (0.6%)] than in the letrozole arm [10/2566 (0.4%)], but the difference was not statistically significant. Of the 16 deaths attributed to a cardiovascular cause in the placebo arm, 12 occurred in the group of 1129 patients who did not switch to letrozole after study unblinding, and 4 occurred in the group of 1448 patients who did switch to letrozole. There was a statistically significant higher incidence of fatal stroke in the letrozole arm [5/2566 (0.2%)] than in the placebo arm (0/2577) (P<0.0001)). (See also **Clinical Trial Adverse Drug Reactions** section).

Musculoskeletal

Bone Mineral Density: Letrozole reduces circulating estrogen levels. The use of estrogen lowering agents, including letrozole, may cause a reduction in bone mineral density (BMD) with a possible consequent increased risk of osteoporosis and fracture. Osteoporosis and/or bone fractures have been reported with the use of letrozole (see also **Special Populations - Geriatrics** and **Clinical Trial Adverse Drug Reactions** sections). Therefore, monitoring of overall bone health is recommended during treatment with letrozole. Women should have their osteoporosis risk assessed and managed according to local clinical practice and guidelines.

In the 5-year, phase III trial for extended adjuvant therapy, after a median follow-up of 28 months, the incidence of self-reported osteoporosis any time after randomization was higher in patients who received letrozole (6.9%) than in patients who received placebo (5.5%) (*P*=0.042). The incidence of clinical fractures any time after randomization was slightly higher in patients who received letrozole than who received placebo (5.9% vs. 5.5% respectively; *P*= 0.548, not statistically significant). Fracture rates any time after randomization in patients with a history of osteoporosis were 10.6% in the letrozole arm compared to 7.3% in the placebo arm; the difference is not statistically significant (*P*= 0.161). In patients with a previous history of fractures, fracture rates were 12.2% in the letrozole arm compared to 8.7% in the placebo arm; the difference is not statistically significant (*P*= 0.177). These results were obtained prior to the study unblinding.

After the study unblinding, patients randomized to the placebo arm were offered to switch to letrozole or discontinue treatment.

The updated results obtained from this phase III trial after unblinding showed that at a median follow-up of approximately 49 months, the incidence of osteoporosis, any time after randomization, was higher in the letrozole arm (12.3%) than in the placebo until switch arm (7.4%) and the letrozole after switch arm (3.6%).

Fracture rates any time after randomization in patients with a history of osteoporosis were 17.7% (55/311) in letrozole arm compared to 10.9% (33/304) in placebo until switch arm and 5.6% (9/162) in the letrozole after switch arm. In patients with a previous history of fractures, fracture rates any time after randomization were 18.1% (52/287) in the letrozole arm compared to 12.2% (37/304) in the placebo arm until switch, and 10.2% (17/167) in the letrozole after switch arm.

The interpretation of the updated results is confounded by the fact that after study unblinding, 56% of patients randomized to placebo opted to switch to letrozole, resulting in different median exposure to treatment (47 months for letrozole, 28 months for placebo until switch and 20 months for letrozole after switch). (See also **Clinical Trial Adverse Drug Reactions** section). The study is ongoing.

Sexual Function/Reproduction

Reproductive Toxicology: Letrozole was evaluated for maternal toxicity as well as embryotoxic, fetotoxic and teratogenic potential in female rats following oral administration of daily doses of 0.003, 0.01 or 0.03 mg/kg on gestation days 6 through 17. Oral administration of letrozole to pregnant rats resulted in teratogenicity and maternal toxicity at 0.03 mg/kg. Embryotoxicity and fetotoxicity were seen at doses of ≥ 0.003 mg/kg and there was an increase in the incidence of fetal malformation among the animals treated. However it is not known whether this was an indirect consequence of the pharmacological activity of letrozole (inhibition of estrogen biosynthesis) or a direct drug effect.

Special Populations

Hepatic Impairment: In a single dose trial with 2.5 mg letrozole in volunteers with hepatic impairment, mean AUC values of the volunteers with moderate hepatic impairment was 37% higher than in normal subjects, but still within the range seen in subjects with normal hepatic function. In a study comparing the pharmacokinetics of letrozole after a single oral dose of 2.5 mg in eight subjects 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} ≥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 should not be given to pregnant women (see **CONTRAINDICATIONS**).

Women of Child-Bearing Potential: There have been post-market reports of spontaneous abortions and congenital anomalies in infants of mothers who have taken letrozole. Letrozole should not be given to women with premenopausal endocrine status (see **CONTRAINDICATIONS**). 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 while being treated with LETROZOLE (see also **Sexual Function/Reproduction, Reproductive Toxicology)**.

Nursing Women: Letrozole should not be administered to nursing mothers (see **CONTRAINDICATIONS**).

Geriatrics: There have been no age-related effects observed on the pharmacokinetics of letrozole.

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 a 5-year, phase III trial for extended adjuvant therapy, after a median follow-up of 28 months, fracture rates recorded any time after randomization in patients 65 years and older were 7.1% (77/1090) in the letrozole arm compared to 7.5 % (77/1033) in the placebo arm; the difference is not statistically significant (P= 0.738). These results were obtained prior to study unblinding.

After the study unblinding, patients randomized to the placebo arm were offered to switch to letrozole or discontinue treatment.

The updated results obtained from this phase III trial after unblinding at a median follow-up of approximately 49 months, showed that the fracture rates any time after randomization in patients 65 years and older were 12.2% (133/1090) in letrozole arm compared to 10.2% (105/1032) in placebo until switch arm and 6.9% (34/495) in letrozole after switch arm.

The interpretation of the updated results is confounded by the fact that after study unblinding, 56% of patients randomized to placebo opted to switch to letrozole, resulting in different median exposure to treatment (47 months for letrozole, 28 months for placebo until switch and 20 months for letrozole after switch). (See also **Clinical Trial Adverse Drug Reactions** section). The study is ongoing.

Monitoring and Laboratory Tests

Plasma Lipids: In the adjuvant setting, the use of aromatase inhibitors, including LETROZOLE, may increase lipid levels (see **Clinical Trial Adverse Drug Reactions** section). Women should have their cholesterol levels assessed and managed according to current clinical practice and guidelines.

NOC/c

ADVERSE REACTIONS

Adverse Drug Reactions Overview

Adverse Events in Adjuvant Study BIG 1-98

The Data and Safety Monitoring Committee, after review of the primary analysis results of the BIG 1-98 study, observed a difference in incidence in grade 5 myocardial infarctions (9 vs. 2 in the letrozole and tamoxifen arms, respectively) and recommended that these cardiac events and certain other safety data be reviewed. As a result, a blinded medical review of more than 2000 patients with pre-specified adverse events (cardiovascular events, fractures, arthritis/arthralgia, myalgia, any adverse event leading to discontinuation) or death without a prior cancer event was conducted following the primary analysis of the adjuvant trial BIG 1-98. This medical review resulted in a change in the cause of death 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. The BIG 1-98 study is currently ongoing, and the medical review is being conducted on an ongoing basis; the updated efficacy and safety results from the study will be made available at the 5-year median treatment duration. It is important to note that these updated safety data will not be comparable with those of the primary analysis. Extrapolation of the absolute risk of these pre-specified events as a function of time cannot be reasonably established.

Letrozole was generally well tolerated as adjuvant treatment of early breast cancer. In the adjuvant setting (26 months median follow-up) approximately 91% vs. 86% of the patients allocated to letrozole or tamoxifen, respectively**,** experienced adverse events. Generally, the observed adverse events were mainly mild or moderate in nature, and most were associated with estrogen deprivation. The most frequently reported adverse events in the adjuvant setting were hot flushes (letrozole: 33.7%, tamoxifen: 38.0%), arthralgia/arthritis (letrozole: 21.2%, tamoxifen 13.5%), and night sweats (letrozole: 14.1%, tamoxifen: 16.4%).

Adverse Events in Extended Adjuvant Study MA-17

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

Letrozole was generally well tolerated as extended adjuvant treatment in women who have received prior standard adjuvant tamoxifen treatment. In the phase III trial for extended adjuvant

therapy, after a median follow-up of 28 months 87.2% vs. 84.5% of the patients on letrozole or placebo experienced adverse events. The most frequent events were: hot flushes (letrozole 49.7% vs. placebo 43.3%), fatigue (lethargy, asthenia, malaise) (letrozole 33.8% vs. placebo 32.2%), arthralgia/arthritis (letrozole 27.7% vs. placebo 22.2%); and sweating (diaphoresis) (24.3% vs. placebo 22.5%).

After the study unblinding, patients randomized to placebo arm were offered to switch to letrozole. The placebo results beyond 28 months median follow-up are confounded by the fact that 56% of patients randomised to placebo opted to switch to letrozole and that dates of onset for general adverse events (based on self-report) were not recorded. In most cases, therefore, it cannot be determined if the adverse events in the placebo group occurred before switch to letrozole or after switch to letrozole. General adverse event data after unblinding of the study should therefore be interpreted with caution.

In the extended adjuvant study after study unblinding at a median follow-up of approximately 49 months the overall incidence of adverse events reported during study treatment or within 30 days irrespective of causality was 94.2% in letrozole, 91.1% in placebo not switched and 94.1% in placebo patients switched to letrozole. The most frequent adverse events were: hot flushes (60.3% in letrozole vs. 52.6% in placebo not switched), fatigue (lethargy, malaise, asthenia) (45.0% in letrozole vs. 44.8% in placebo not switched), arthralgia/arthritis (37.9% in letrozole vs. 26.8% in placebo not switched), sweating (diaphoresis) (34.0% in letrozole vs. 29.8% in placebo not switched).

Most frequently reported adverse events from the clinical trials in adjuvant and extended adjuvant are summarized in Tables 1, 2 and 3.

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

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 letrozole can be expected to experience adverse reactions. The most frequently reported adverse reactions in the clinical trials were hot flushes, nausea and fatigue. Many adverse reactions can be attributed to the normal physiological consequences of estrogen deprivation (e.g., hot flushes, alopecia and vaginal bleeding). The adverse drug reactions reported from clinical trials are summarized for first-line and second-line treatment with letrozole.

Clinical Trial Adverse Drug Reactions

Adverse Events in Adjuvant Treatment of Early Breast Cancer in Postmenopausal Women

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

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 (82%) were grade 1 and grade 2 applying the Common Toxicity Criteria Version 2.0. Serious adverse events that were suspected to be related to study treatment were significantly less frequent with letrozole (177 patients, 4.5%) than with tamoxifen (276 patients, 6.9%). Table 1 describes the most frequently reported adverse events irrespective of relationship to study treatment in the adjuvant BIG 1-98 trial (safety population, during treatment or within 30 days of stopping treatment).

In the adjuvant setting, total cholesterol levels remained stable over 5 years (median 1-3% decrease) in the letrozole arm whereas there was an expected slight decrease (median 10-15% decrease) over time observed in the tamoxifen arm. Hypercholesterolemia recorded at least once as a check-listed adverse event was more frequent in patients treated with letrozole (43%) compared with tamoxifen (19%). Hypercholesterolemia recorded 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 one time. The incidence of laboratory evaluated hypercholesterolemia was more frequent in patients treated with letrozole (5.6%) compared to tamoxifen (1.3%) (see Table 1).

Overall, the incidence of cardiovascular events was similar in the letrozole and tamoxifen arms (9.7 vs. 10.5%, respectively), although more patients receiving letrozole compared to tamoxifen were reported to have cardiac failure (0.9 vs. 0.4%, respectively), myocardial infarction (0.8 vs. 0.4%, respectively), fatal cardiac events (0.6 vs. 0.3%, respectively), and numerically higher fatal stroke (0.15%, 6 cases vs. 0.03%, 1 case, respectively). As expected, thromboembolic events were more frequent in patients on tamoxifen compared to letrozole (3.0 vs. 1.4%), respectively.

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

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

Letrozole treatment was associated with a significantly higher risk of osteoporosis (2.0 vs. 1.1% with tamoxifen). Bone fractures were significantly higher in the letrozole arm than the tamoxifen arm (5.7 vs. 4.0%, respectively).

Table 1 - Most frequently reported adverse events irrespective of relationship to study drug in the Adjuvant Trial BIG 1-98

	Letrozole	**Tamoxifen**
	N=3975	**N=3988**
Preferred Term	**n (%)**	**n (%)**
Hot flashes/flushes	1338 (33.7)	1515 (38.0)
Arthralgia/Arthritis	841 (21.2)	537 (13.5)
Night sweats	561 (14.1)	654 (16.4)
Nausea	378 (9.5)	418 (10.5)
Fatigue (lethargy,malaise,asthenia)	333 (8.4)	345 (8.7)

Table 1 - Most frequently reported adverse events irrespective of relationship to study drug in the Adjuvant Trial BIG 1-98

Edema	286 (7.2)	288 (7.2)
Myalgia	256 (6.4)	243 (6.1)
Bone fractures	226 (5.7)	161 (4.0)
Hypercholesterolemia[1,2]	173 (5.6)	40 (1.3)
Vaginal bleeding	177 (4.5)	413 (10.4)
Depression	144 (3.6)	155 (3.9)
Headache	143 (3.6)	126 (3.2)
Vaginal irritation	139 (3.5)	122 (3.1)
Vomiting	109 (2.7)	107 (2.7)
Dizziness/light-headedness	97 (2.4)	112 (2.8)
Osteoporosis	80 (2.0)	44 (1.1)
Constipation	59 (1.5)	95 (2.4)
Cataract	48 (1.2)	39 (1.0)
Breast Pain	40 (1.0)	47 (1.2)
Cardiac failure	36 (0.9)	15 (0.4)
Anorexia	33 (0.8)	31 (0.8)
Myocardial infarction	31 (0.8)	17 (0.4)
Angina pectoris	27 (0.7)	24 (0.6)
Ovarian cyst	17 (0.4)	14 (0.4)
Endometrial proliferation disorders	10 (0.3)	73 (1.8)
Other endometrial disorders	3 (<0.1)	4 (0.1)

[1] Based on number of patients with normal serum cholesterol levels at baseline and developing at least one value greater than 1.5 times the upper limit of normal in the laboratory, measuring total serum cholesterol. Approximately 90% of the measured values were non-fasting measurements.

[2] Denominator is number of patients with baseline measurements of total serum cholesterol – letrozole, n=3105; tamoxifen, n=3129.

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

Table 2 below describes the adverse events occurring at a frequency of at least 2% in any treatment group in a well-controlled clinical study in which over 5100 postmenopausal patients with receptor-positive or unknown primary breast cancer patients who had remained disease-free after completion of adjuvant treatment with tamoxifen were randomly assigned either letrozole or placebo. The median duration of extended adjuvant treatment was 24 months and the median duration of follow-up for safety was 28 months for patients receiving letrozole and placebo**.** Most adverse events reported were grade 1 or grade 2 based on the Common Toxicity Criteria Version 2.0.

Table 2 - Most frequently reported adverse events irrespective of relationship to study drug (median treatment duration 24 months) in the Extended Adjuvant Trial MA-17

	Letrozole N= 2563 n (%)	**Placebo N= 2573 n (%)**
Any adverse event	2234 (87.2)	2174 (84.5)
Cardiac disorders	90 (3.5)	113 (4.4)
Eye disorders	91 (3.6)	79 (3.1)
Gastrointestinal	725 (28.3)	731 (28.4)
Constipation	290 (11.3)	304 (11.8)
Nausea	221 (8.6)	212 (8.2)
Diarrhea NOS	128 (5.0)	143 (5.6)
Abdominal pain NOS	74 (2.9)	86 (3.3)
Vomiting NOS	75 (2.9)	83 (3.2)
Dyspepsia	72 (2.8)	82 (3.2)
General disorders	1155 (45.1)	1090 (42.4)
Asthenia	862 (33.6)	826 (32.1)
Edema NOS	471 (18.4)	416 (16.2)
Chest pain	59 (2.3)	69 (2.7)
Pain NOS	56 (2.2)	47 (1.8)
Infections and Infestations	166 (6.5)	163 (6.3)
Investigation	184 (7.2)	147 (5.7)
Weight increased	55 (2.1)	51 (2.0)
Weight decreased	52 (2.0)	38 (1.5)
Metabolism and nutrition disorders	551 (21.5)	537 (20.9)
Hypercholesterolaemia	401 (15.6)	398 (15.5)
Anorexia	119 (4.6)	96 (3.7)
Musculoskeletal disorders	978 (38.2)	836 (32.5)
Arthralgia	565 (22.0)	465 (18.1)
Arthritis NOS	173 (6.7)	124 (4.8)
Myalgia	171 (6.7)	122 (4.7)
Fractures	152 (5.9)	142 (5.5)
Back pain	129 (5.0)	112 (4.4)
Bone pain	70 (2.7)	81 (3.1)
Pain in extremity	70 (2.7)	62 (2.4)
Neoplasms benign, malignant and unspecified	51 (2.0)	48 (1.9)
Nervous system disorders	865 (33.7)	819 (31.8)
Headache	516 (20.1)	508 (19.7)
Dizziness	363 (14.2)	342 (13.3)
Psychiatric disorders	320 (12.5)	276 (10.7)
Insomnia	149 (5.8)	120 (4.7)
Depression	115 (4.5)	104 (4.0)
Anxiety	78 (3.0)	73 (2.8)
Renal disorders	130 (5.1)	100 (3.9)
Reproductive disorders	303 (11.8)	357 (13.9)
Vulvovaginal dryness	137 (5.3)	127 (4.9)
Vaginal haemorrhage	123 (4.8)	171 (6.6)

Table 2 - Most frequently reported adverse events irrespective of relationship to study drug (median treatment duration 24 months) in the Extended Adjuvant Trial MA-17

	Letrozole N= 2563 n (%)	**Placebo N= 2573 n (%)**
Respiratory Disorders	280 (10.9)	261 (10.1)
Dyspnoea	140 (5.5)	137 (5.5)
Cough	96 (3.7)	94 (3.7)
Skin disorders	830 (32.4)	787 (30.6)
Sweating increased	619 (24.2)	577 (22.4)
Alopecia	112 (4.4)	83 (3.2)
Rash NOS	41 (1.6)	53 (2.1)
Vascular disorders	1376 (53.7)	1230 (47.8)
Flushing[1]	1273 (49.7)	1114 (43.3)
Hypertension NOS	122 (4.8)	110 (4.3)
Lymphoedema NOS	68 (2.7)	79 (3.1)

[1] Includes terms "hot flashes/hot flushes".
NOS : Not Otherwise Specified

The incidence of self-reported osteoporosis from the MA-17 core study was significantly higher in patients who received letrozole 6.9% (176) than in patients who received placebo 5.5% (141) (*P*=0.042). The incidence of clinical fractures was 5.9% (152) in patients who received letrozole compared to 5.5% (142) in patients who received placebo, the difference is not statistically significant (*P*=0.548).

Results (median duration of follow-up was 20 months) from the MA-17 bone sub-study demonstrated that, at 2 years, compared to baseline, patients receiving letrozole had a mean decrease (versus baseline) of 3% versus 0.4% (*P*=0.048) in placebo for hip bone mineral density. There was no significant difference in terms of lumbar spine bone mineral density.

The incidence of cardiovascular ischemic events from the MA-17 core study was comparable between patients who received letrozole 6.8% (175) and placebo 6.5% (167) (*P*=NS).

Results from the MA-17 lipid study (median follow-up 36 months) did not show significant differences between the letrozole and placebo groups. Subjects did not have a prior history of hyperlipidemia. The study continues to investigate the long term impact of letrozole on lipid levels. As per normal clinical practice and guidelines for post-menopausal women, physicians should continue their routine monitoring of lipid levels on a regular basis.

Adverse Events in Extended Adjuvant Therapy in Early Breast Cancer, Median Treatment Duration of 47 Months and a Median Follow-up of 49 Months

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

Table 3 below compares the self-reported adverse events irrespective of drug relationship experienced in the randomized letrozole arm at a median treatment duration of 24 months and 47

months. The table describes the adverse events occurring in the safety population at a cut-off frequency of at least 2%. Most of these adverse events were grade 1 or grade 2 based on Common Toxicity Criteria Version 2.0. The placebo comparison after unblinding is not reliable due to the fact that 56% of patients randomized to placebo opted to switch to letrozole and dates of onset for general adverse events (based on self-report) were not recorded. In most cases, therefore, it cannot be determined if the adverse events in the placebo group occurred before switch to letrozole or after switch to letrozole. The safety population after study unblinding consists of 2566 patients in the letrozole arm, 1129 patients in the placebo not switched arm and 1448 patients in the letrozole after switch from placebo arm. The median 24 months of treatment duration versus the median 47 months of treatment duration comparison is presented to indicate the evolution of adverse events in the letrozole arm over time.

Table 3 - Most frequently reported adverse events irrespective of relationship to study drug in the Extended Adjuvant Trial MA-17

	Letrozole (median treatment duration 24 months) N= 2563 n (%)	**Letrozole (median treatment duration 47 months) N= 2566 n (%)**
Any adverse event	2234 (87.2)	2418(94.2)
Cardiac disorders	90 (3.5)	135 (5.3)
Eye disorders	91 (3.6)	138 (5.4)
Gastrointestinal	725 (28.3)	1030 (40.1)
Constipation	290 (11.3)	432 (16.8)
Nausea	221 (8.6)	355 (13.8)
Diarrhea NOS	128 (5.0)	199 (7.8)
Vomiting	75 (2.9)	116 (4.5)
Abdominal pain NOS	74 (2.9)	112 (4.4)
Dyspepsia	72 (2.8)	122 (4.8)
Flatulence	47 (1.8)	55 (2.1)
General disorders	1155 (45.1)	1462 (57.0)
Asthenia	862 (33.6)	1139 (44.4)
Edema NOS	471 (18.4)	632 (24.6)
Chest pain	59 (2.3)	83 (3.2)
Pain NOS	56 (2.2)	68 (2.7)
Edema peripheral	41 (1.6)	59 (2.3)
Fatigue	9 (0.4)	51 (2.0)
Infections and Infestations	166 (6.5)	251 (9.8)
Investigation	184 (7.2)	251 (9.8)
Weight increased	55 (2.1)	69 (2.7)
Weight decreased	52 (2.0)	74 (2.9)
Metabolism and nutrition disorders	551 (21.5)	811 (31.6)
Hypercholesterolaemia	401 (15.6)	582 (22.7)
Anorexia	119 (4.6)	178 (6.9)
Hyperglycaemia NOS	48 (1.9)	78 (3.0)
Musculoskeletal disorders	978 (38.2)	1288 (50.2)
Arthralgia	565 (22.0)	806 (31.4)

Table 3 - Most frequently reported adverse events irrespective of relationship to study drug in the Extended Adjuvant Trial MA-17

	Letrozole (median treatment duration 24 months) N= 2563 n (%)	**Letrozole (median treatment duration 47 months) N= 2566 n (%)**
Arthritis NOS	173 (6.7)	349 (13.6)
Myalgia	171 (6.7)	318 (12.4)
Fractures	152 (5.9)	279 (10.9)
Back pain	129 (5.0)	162 (6.3)
Bone pain	70 (2.7)	157 (6.1)
Pain in extremity	70 (2.7)	90 (3.5)
Muscle cramp	39 (1.5)	52 (2.0)
Neoplasms benign, malignant and unspecified	51 (2.0)	83 (3.2)
Nervous system disorders	865 (33.7)	1200 (46.8)
Headache	516 (20.1)	792 (30.9)
Dizziness	363 (14.2)	547 (21.3)
Sensory disturbance NOS	41 (1.6)	65 (2.5)
Hypoaesthesia	41 (1.6)	60 (2.3)
Memory impairment	35 (1.4)	52 (2.0)
Psychiatric disorders	320 (12.5)	425 (16.6)
Insomnia	149 (5.8)	204 (8.0)
Depression	115 (4.5)	158 (6.2)
Anxiety	78 (3.0)	103 (4.0)
Renal disorders	130 (5.1)	172 (6.7)
Pollakiuria	47 (1.8)	65 (2.5)
Incontinence NOS	45 (1.8)	56 (2.2)
Reproductive disorders	303 (11.8)	412 (16.1)
Vulvovaginal dryness	137 (5.3)	184 (7.2)
Vaginal haemorrhage	123 (4.8)	157 (6.1)
Respiratory Disorders	280 (10.9)	396 (15.4)
Dyspnoea	140 (5.5)	208 (8.1)
Cough	96 (3.7)	141 (5.5)
Skin disorders	830 (32.4)	1117 (43.5)
Sweating increased	619 (24.2)	867 (33.8)
Alopecia	112 (4.4)	147 (5.7)
Dry skin	42 (1.6)	59 (2.3)
Rash NOS	41 (1.6)	58 (2.3)
Dermatitis exfoliative NOS	34 (1.3)	54 (2.1)
Vascular disorders	1376 (53.7)	1662 (64.8)
Flushing[1]	1273 (49.7)	1548 (60.3)
Hypertension NOS	122 (4.8)	178 (6.9)
Lymphoedema NOS	68 (2.7)	91 (3.5)

[1] Includes terms “hot flashes/hot flushes”.

NOS : Not Otherwise Specified

The most frequent adverse events irrespective of drug relationship (cut-off frequency of at least 2%) reported in the 604/2566 (23.5%) patients randomized to the letrozole arm who had actually completed 5 years of treatment were: flushing (384, 64%), asthenia (288, 47.4%), increased sweating (241, 40%), headache (221, 37%), arthralgia (220, 36%), hypercholesterolemia (187, 31%), edema NOS (160, 26.5%) and dizziness (145, 24%).

In contrast to general self-reported adverse events presented in the table above, dates of onset were recorded for serious adverse events (SAE) and for targeted adverse events of fracture, osteoporosis and cardiovascular events. The comparison between the letrozole randomized arm to placebo until switch is therefore more meaningful for these events.

Osteoporosis and fracture

After the study unblinding, patients randomized to the placebo arm were offered to switch to letrozole or discontinue treatment.

The updated results from the MA-17 core safety population obtained after unblinding, showed that at a median follow-up of 49 months, the incidence of osteoporosis any time after randomization was higher in patients originally randomized in the letrozole arm than for patients in the placebo until switch arm [12.3% in letrozole arm vs. 7.4% in placebo until switch arm (P<0.001)].

The incidence of bone fractures, any time after randomization, was significantly higher in patients who received letrozole than for placebo until switch (10.9% vs. 7.2%, respectively). In the placebo patients who switched to letrozole, newly diagnosed osteoporosis, any time after switching, was reported in 3.6% while fractures were reported in 5.1% any time after switching.

In the randomized letrozole arm, 1.9% of patients experienced more than one fracture, compared with 1.1% in the placebo until switch group and 1.0% in the letrozole after switch from placebo group. Of the 74/1448 patients who experienced a fracture after switching to letrozole from placebo, 12 patients had previously experienced a fracture on placebo (and 3 of these patients had experienced more than one fracture on placebo).

The interpretation of the updated results in the core study is confounded by the fact that after study unblinding, 56% of patients randomized to placebo opted to switch to letrozole, resulting in different median exposure to treatment (47 months for letrozole, 28 months for placebo until switch and 20 months for letrozole after switch from placebo).

Updated results (median follow-up was 40 months) from the bone mineral density (BMD) sub-study conducted in a subset of 219 patients (117 on letrozole and 102 on placebo, including 77 placebo/letrozole switchers), demonstrated that, at 2 years, compared to baseline, patients receiving letrozole had a median decrease of 3.8% in hip BMD compared to 2.0% in the placebo until switch group (P=0.018). There were no statistically significant differences in median % changes from baseline in hip BMD at any other measured time-points other than at 2 years. There were no statistically significant changes in lumbar spine BMD at any time between letrozole and placebo until switch groups. In the 77 placebo patients who switched to letrozole,

BMD in the hip and lumbar spine showed a median decrease from baseline of approximately 1-2% at each of the first, second and third annual visits after switching to letrozole. The treatment duration in each group was median 38 months for letrozole, 22 months for placebo until switch and 22 months for letrozole after switch from placebo respectively. (See also **WARNINGS AND PRECAUTIONS, Musculoskeletal** and **Special Populations - Geriatrics** sections**)**.

Cardiovascular events

As reported in Table 4 below, at a median follow-up of 49 months, the incidence of cardiovascular events any time after randomization was 11.1% for letrozole versus 8.6% for placebo until switch. This is higher than the incidence reported at 28 months follow-up (6.8% in the letrozole arm compared with 6.5% in the placebo arm, see also **WARNINGS AND PRECAUTIONS, Cardiovascular** section**)**.

Table 4 - Cardiovascular disease any time after randomization in the MA-17 study (safety population), median follow-up of 49 months

	Letrozole	**Placebo until switch [1]**	**Letrozole after switch [2]**
	N=2566 n (%)	**N=2577 n (%)**	**N=1448 n (%)**
Cardiovascular disease			
No	2280 (88.9)	2355 (91.4)	1392 (96.1)
Yes	286 (11.1)	222 (8.6)	56 (3.9)
Type of cardiovascular disease			
Angina requiring CABG	12 (0.5)	13 (0.5)	2 (0.1)
Myocardial Infarction	34 (1.3)	24 (0.9)	4 (0.3)
New or worsening angina	44 (1.7)	32 (1.2)	6 (0.4)
Angina requiring PTCA	14 (0.5)	11 (0.4)	
Thromboembolic event	25 (1.0)	16 (0.6)	7 (0.5)
Stroke/transient ischemic attack	43 (1.7)	33 (1.3)	6 (0.4)
Other	179 (7.0)	140 (5.4)	35 (2.4)
Arrhythmia	103 (4.0)	85 (3.3)	16 (1.1)
Cardiac	66 (2.6)	51 (2.0)	11 (0.8)
Vascular	28 (1.1)	21 (0.8)	4 (0.3)
Valvular	9 (0.4)	5 (0.2)	3 (0.2)
CNS/Cerebrovascular	7 (0.3)	3 (0.1)	0
Other	8 (0.3)	11 (0.4)	7 (0.5)

[1] After randomization but until switch to letrozole, if switch occurred; if switch did not occur, then until date of last contact.
[2] After switch until date of last contact.

The most frequent cause of non-cancer death during study treatment or within 30 days of stopping treatment (regardless of treatment arm) was cardiovascular. (See **Warnings and Precautions, Cardiovascular** section).

The incidence of serious adverse events (all grades 1-5) regardless of study drug relationship was 0.5% in the letrozole group, 1.3% in the placebo not switched arm and 0.3% in letrozole after switch arm. Breast cancer related death reported during treatment or within 30 days of stopping

treatment occurred in 0.5% of patients in the letrozole arm, 0.8% in the placebo not switched arm and 0.3% in the letrozole after switch arm. Non-breast cancer related death reported during treatment or within 30 days of stopping treatment occurred in 1.7% of patients in the letrozole arm, 2.6% in the placebo not switched arm and 0.5% in the letrozole after switch arm.

Lipids
Updated results (median follow-up was approximately 50 months) from the lipid sub-study showed no significant differences between the letrozole and placebo groups at any time.

The MA-17 study is ongoing. The final study results are pending.

Adverse Events in First-Line Therapy

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

Table 5 below shows the frequency of adverse events considered possibly related to trial drug that have been reported with an incidence of more than 2.0% (whether for letrozole or for tamoxifen) in a well-controlled clinical study with letrozole (2.5 mg daily) and tamoxifen (20 mg daily).

Table 5

Adverse Event **System Organ Class/Preferred Term**	**Letrozole** **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		
Appetite Decreased	1.6	3.3
Appetite Increased	1.8	2.0
Nervous System Disorders		
Headache	2.2	2.4
Skin and Subcutaneous Tissue Disorders		
Alopecia	5.5	3.3
Sweating Increased	2.0	2.9
Vascular Disorders		
Hot Flushes	16.7	14.3
Thromboembolic Events	1.5	1.9

Adverse Events in Second-Line Therapy

Table 6 below shows in decreasing order of frequency the AEs - considered possibly related to trial drug according to the investigator - that have been reported with an incidence of more than 1.0% for letrozole in a controlled clinical trial with letrozole (2.5 mg daily) and megestrol acetate (160 mg daily) for up to 33 months.

Table 6

Adverse Event	**Letrozole % (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 flushes	5.2	3.7
Hair thinning	3.4	1.1
Rash[1]	3.4	0.5
Vomiting	2.9	1.6
Dyspepsia	2.9	1.6
Weight increase	2.3	8.5
Musculoskeletal pain[2]	2.3	1.1
Anorexia	2.3	1.1
Vaginal bleeding	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
Increased sweating	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

Spontaneously reported adverse drug reactions are presented below. Because these 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 letrozole exposure.

Blood and lymphatic system disorders	Leukopenia
Cardiac disorders	Palpitations, tachycardia, 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, hepatitis
Immune system disorders	Anaphylactic reaction
Infections and infestations	Urinary tract infection
Investigations	Weight increase, weight loss, increase in aminotransferases
Musculoskeletal and connective tissue disorders	Myalgia, osteoporosis, bone fractures
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Tumour pain
Nervous system disorders	Memory impairment, dysesthesia[1], taste disturbance, cerebrovascular accident
Psychiatric disorders	Anxiety[2]
Renal and urinary disorders	Increased urinary frequency
Reproductive system and breast disorders	Vaginal discharge
Respiratory, thoracic and mediastinal disorders	Cough
Skin and subcutaneous tissue	Rash[3], pruritis, dry skin, urticaria, angioedema, erythema
Disorders	multiforme, toxic epidermal necrolysis
Vascular disorders	Thrombophlebitis[4], hypertension, pulmonary embolism, arterial thrombosis, cerebrovascular infarction, ischemic cardiac events

[1] Including paresthesia, hypoesthesia
[2] Including nervousness, irritability
[3] Including erythematous, maculopapular, psoriaform and vesicular rash
[4] Including superficial and deep thrombophlebitis

DRUG INTERACTIONS

Drug-Drug Interactions

Clinical trials of interaction with letrozole and cimetidine or warfarin indicate that coadministration does not result in clinically significant drug interactions.

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

In vitro, letrozole inhibits the cytochrome P450 isoenzymes 2A6 and moderately 2C19. CYP2A6 does not play a major role in drug metabolism. In *in vitro* experiments letrozole was not able to substantially inhibit the metabolism of diazepam (a substrate of CYP2C19) at concentrations approximately 100-fold higher than those observed in plasma at steady-state. Thus clinically relevant interactions with CYP2C19 are unlikely to occur. However, caution should be used in the concomitant administration of drugs whose disposition is mainly dependent on these isoenzymes and whose therapeutic index is narrow.

Use with Other Anticancer Agents: Co-administration of letrozole 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 letrozole in combination with other anticancer 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.

NOC/c **DOSAGE AND ADMINISTRATION**

Dosing Considerations

- Insufficient data available to recommend dose adjustment in patients with severe hepatic impairment (see **Patients with hepatic and/or renal impairment**).

Recommended Dose and Dosage Adjustment

Adult and Elderly Patients: The recommended dose is one 2.5 mg tablet once daily. No dose adjustment is required for elderly patients.

In the adjuvant setting, the intended duration of treatment is 5 years, although data are limited to a median follow-up of 26 months.

In the extended adjuvant setting, treatment with LETROZOLE (letrozole) is intended for 5 years, although scientific evidence collected to date covers a median follow-up of 49 months.

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

Patients with hepatic and/or renal impairment: No dosage adjustment is required for patients with renal impairment (creatinine clearance ≥10 mL/min) or moderate hepatic impairment. Insufficient data are available to recommend a dose adjustment in breast cancer patients with severe non-metastatic hepatic impairment. Therefore, patients with severe hepatic impairment (Child-Pugh score C) should be kept under close supervision for adverse events (see **WARNINGS AND PRECAUTIONS** section).

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. Do not double doses.

OVERDOSAGE

Isolated cases of letrozole overdose have been reported. In these instances, the highest single dose ingested was 62.5 mg or 25 tablets. While no serious adverse events were reported in these cases, because of the limited data available, no firm recommendations for treatment can be made. 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.

For management of suspected drug overdose, contact your regional poison control centre. 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.

NOC/c

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

LETROZOLE (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

Letrozole exerts its antitumour 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.

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 (V_{dss} = 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. 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 terminal elimination half-life in plasma is about 2 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.

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 yellow, round, film-coated, biconvex tablet that is debossed “2.5” on one side and plain on the reverse side contains the medicinal ingredient letrozole (2.5 mg) and non-medicinal ingredients FD&C Yellow #6 aluminium lake, magnesium stearate, polyethylene glycol, polyvinyl alcohol, silicified microcrystalline cellulose, sodium starch glycollate, talc, titanium dioxide and yellow iron oxide.

Available in blister packages containing 28 tablets.

PART II: SCIENTIFIC INFORMATION

LETROZOLE, indicated for:

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

has been issued market authorization with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the market authorization granted.

LETROZOLE, indicated for:

- The first-line therapy in postmenopausal women with advanced breast cancer;
- The hormonal treatment of advanced/metastatic breast cancer in women with natural or artificially-induced postmenopausal status, who have disease progression following antiestrogen therapy;

has been issued market authorisation without conditions.

LETROZOLE should be administered under the supervision of a qualified physician experienced in the use of anti-cancer agents.

PHARMACEUTICAL INFORMATION

Drug Substance

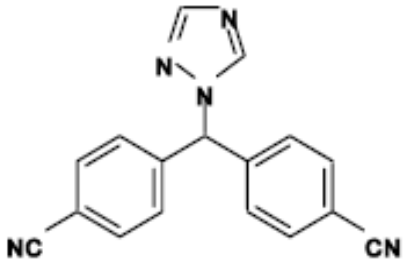
Proper name: Letrozole

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

Comparative Bioavailability Study

A two-way, single-dose, randomized, double-blind, crossover comparative oral bioavailability study was conducted in healthy adult female post-menopausal volunteers under fasting conditions. The results obtained from 12 subjects are presented in Table 7.

Table 7
letrozole
1 x 2.5 mg Letrozole Tablet
From measured data
uncorrected for potency

Parameter[Ŧ]	Geometric Mean Arithmetic Mean (CV %)		Ratio of Geometric Means (%)	90% Confidence Interval (%)
	Test LETROZOLE (letrozole) 2.5 mg Tablet	Reference FEMARA® (letrozole) 2.5 mg Tablet[¥]		
AUC_{72} (ng.h/mL)	915.88 929.11 (17.53)	906.18 916.96 (15.79)	101.07	98.55 – 103.65
C_{max} (ng/mL)	38.99 40.02 (23.78)	37.83 38.38 (17.11)	103.05	95.16 – 111.60
T_{max}[§] (h)	1.00 (0.75 – 1.75)	1.13 (0.75 – 5.00)		

[§] Expressed as median and range
[¥] Manufactured by Novartis Pharmaceuticals Canada Inc.
[Ŧ] AUC_I and $T_{1/2}$ are not reported: these parameters could not be accurately estimated due to long half-life of the active ingredient and the design of the study.

NOC/c **Adjuvant Treatment of Early Breast Cancer in Postmenopausal Women**

A multicenter, double-blind study randomized over 8000 postmenopausal women with resected receptor-positive early breast cancer to one of the following arms:

A. tamoxifen for 5 years

B. letrozole for 5 years

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

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

Selected baseline characteristics for the study population are shown in Table 8.

Table 8- Selected Study Population Demographics for Adjuvant Study (ITT population)

Baseline Status	Letrozole N=4003	Tamoxifen N=4007
Age (median, years)	61	61
Age range (years)	38-89	39-90
Hormone receptor status (%)		
ER+ and/or PgR+	99.7	99.7
Both unknown	0.3	0.3
Nodal status (%)		
Node negative	52	52
Node positive	41	41
Nodal status unknown	7	7
Prior adjuvant chemotherapy (%)	25	25

Patients have been followed for a median of 26 months, 76% of the patients for more than 2 years, and 15% (1197 patients) for 5 years or longer.

The primary endpoint of the trial was disease-free survival (DFS) which was assessed as the time from randomization to the earliest event of loco-regional or distant recurrence (metastases) of the primary disease, development of invasive contralateral breast cancer, appearance of a second non-breast primary tumour or death from any cause. In the overall population, letrozole reduced the risk of recurrence by 19% compared with tamoxifen (hazard ratio 0.81; *P*=0.003). The 5-year DFS rates were 84.0% for letrozole and 81.4% for tamoxifen (absolute difference 2.6%). In the overall population, letrozole also significantly reduced the risk of recurrence compared with tamoxifen whether prior adjuvant chemotherapy was given (hazard ratio 0.72; *P*=0.018) or not (hazard ratio 0.84; *P*=0.044).

However, a pre-planned, not powered, subset analysis revealed that DFS advantage over tamoxifen was demonstrated in those patients with node positive disease (HR 0.71; 95% CI 0.59-0.85, *P*=0.0002) and was not observed in patients with node negative disease (HR 0.98; 95% CI 0.77-1.25, *P*=0.89), with significant treatment by nodal status interaction.

For the secondary endpoint, overall survival, a total of 358 deaths were reported (166 on letrozole and 192 on tamoxifen). There was no significant difference between treatments in overall survival (hazard ratio 0.86; *P*=0.15).

Distant disease-free survival (distant metastases), a surrogate for overall survival, differed significantly overall. There was a 27% reduction in the risk in the letrozole group (hazard ratio 0.73; *P*=0.001).

Letrozole reduced the risk of invasive contralateral breast cancer by almost 40% (19 vs. 31 on letrozole and tamoxifen arms, respectively), but likely due to the low number of events, this result was not statistically significant. Patients receiving letrozole, compared to tamoxifen, had fewer second malignancies (1.9% vs. 2.4%). Particularly the incidence of endometrial cancer was lower with letrozole compared to tamoxifen (0.1% vs. 0.4%).

Data in Table 9 and Figures 1 and 2 reflect results from non-switching arms (arms A and B) together with data truncated 30 days after the switch in the two switching arms (arms C and D). The analysis of monotherapy vs. sequencing of endocrine treatments will be conducted when the necessary number of events has been achieved.

Table 9– Disease-Free and Overall Survival (ITT Population)

	letrozole N=4003	**tamoxifen** N=4007	**Hazard Ratio (95 % CI)**	**P-Value**
Disease-free survival[1]	351	428	0.81 (0.70, 0.93)	0.003
o Node positive			0.71 (0.59, 0.85)	0.0002
o Node negative			0.98 (0.77, 1.25)	0.888
o Prior adjuvant chemotherapy			0.72 (0.55, 0.95)	0.018
o No chemotherapy			0.84 (0.71, 1.00)	0.044
Distant disease-free survival[2]	184	249	0.73 (0.60, 0.88)	0.001
o Node positive			0.67 (0.54, 0.84)	0.0005
o Node negative			0.90 (0.60, 1.34)	0.597
o Prior adjuvant chemotherapy			0.69 (0.50, 0.95)	0.024
o No chemotherapy			0.75 (0.60, 0.95)	0.018
Systemic disease-free survival[3]	323	383	0.83 (0.72, 0.97)	0.016
Contralateral breast cancer	19	31	0.61 (0.35, 1.08)	0.091
Overall survival	166	192	0.86 (0.70, 1.06)	0.155
o Node positive			0.81 (0.63, 1.05)	0.113
o Node negative			0.88 (0.59, 1.30)	0.507
o Prior adjuvant chemotherapy			0.76 (0.51, 1.14)	0.185
o No chemotherapy			0.90 (0.71, 1.15)	0.395

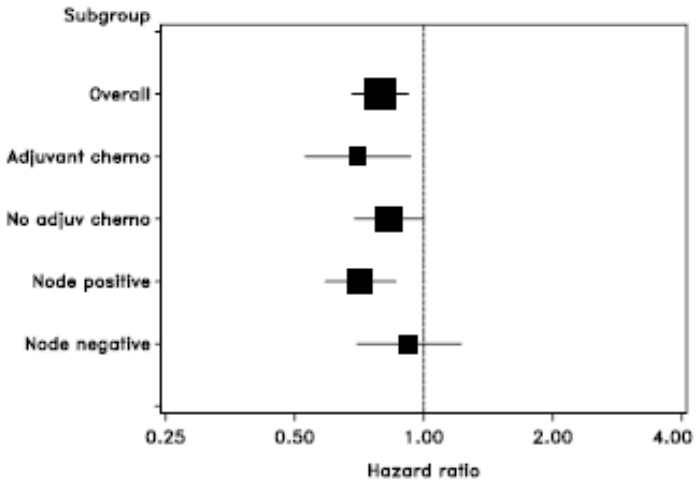
Definition of

[1] Disease-free survival: Time from randomization to the earliest occurrence of invasive loco-regional recurrence, distant metastases, invasive contralateral breast cancer, or death from any cause.

[2] Distant disease-free survival: Time from randomization to distant metastases.

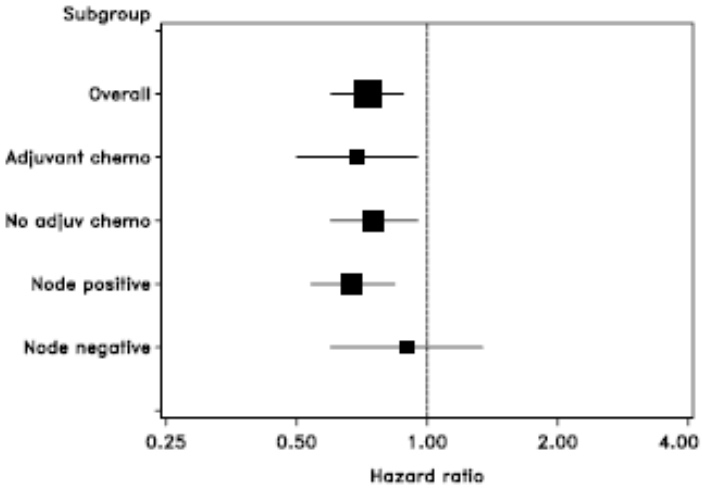
[3] Systemic disease-free survival: Time from randomization to invasive regional recurrence, distant metastases, or death from any cause.

Figure 1: Forest plot for DFS by subgroup



Favours Letrozole Favours Tamoxifen

Figure 2: Forest plot for distant disease-free survival by subgroup



Favours Letrozole Favours Tamoxifen

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

NOC/c **Extended Adjuvant Therapy in Early Breast Cancer, Median Treatment Duration of 24 Months, Median Follow-up of 28 Months**

The MA-17 trial was a multicenter, double-blind, randomized, placebo-controlled trial, performed in over 5100 postmenopausal women with receptor-positive (or unknown) primary breast cancer. Patients who had remained disease-free after prior standard adjuvant treatment

with tamoxifen (4.5-6 years) were randomly assigned either letrozole or standard of care (placebo).

The planned duration of treatment for patients in the MA-17 study was 5 years. At the time of the primary efficacy analysis, median duration of follow-up was 28 months. Approximately 25% of patients had completed 3 or more years of treatment. When the primary efficacy endpoint was met according to the prospective, pre-specified statistical plan, the study was recommended to be unblinded by the Independent Data and Safety Monitoring Committee and patients from the placebo group were offered letrozole. The MA-17 trial continues as an open-label study with on going follow-up for safety and efficacy analyses for the full duration of the trial..

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 or development of contralateral breast cancer. (The protocol definition excluded deaths.) The secondary endpoints included: overall survival (OS), rate of contralateral breast cancer, and other clinical and laboratory safety parameters.

Letrozole was shown to reduce the risk of recurrence by 42% compared with placebo (hazard ratio 0.58; *P*=0.00003). Sensitivity analysis confirmed the robustness of the data. The statistically significant benefit in DFS in favour of letrozole was observed regardless of nodal status (node negative, hazard ratio 0.48, *P*=0.002; node positive, hazard ratio 0.61, *P*=0.002).

The risk of distant metastases was significantly lower with letrozole than with placebo, hazard ratio 0.61 (39% lower risk; 95% CI 0.44, 0.84; *P*=0.003).

Overall survival was a secondary endpoint and data collected to date is premature, therefore, no definitive conclusions on overall survival can be made.

At the time of unblinding of the study and optional switch to letrozole (median follow-up of 28 months), a total of 113 deaths were reported (51 in the letrozole arm and 62 in the placebo arm). In the overall population, there was no significant difference in OS between treatment arms (hazard ratio 0.82 (CI: 0.56, 1.19); *P* =0.291).

In node-positive disease (median follow-up of 28 months), letrozole significantly reduced the risk of mortality by approximately 40% (hazard ratio 0.61 (CI 0.38, 0.97); *P* =0.035). At an updated safety analysis (median follow-up of 30 months), reduction in mortality was no longer statistically significant: 36/1184 (3.0%) in the letrozole arm compared to 53/1187 (4.5%) in the placebo arm (hazard ratio 0.67 (CI 0.44, 1.02); *P* =0.058).

In node-negative patients (median follow-up of 28 months), there was an insignificant increase in the number of deaths on the letrozole arm 19/1298 (1.5%) compared to the placebo arm 14/1301 (1.1%), [hazard ratio 1.36 (CI 0.68, 2.71); *P* =0.385, NS]. At an updated safety analysis (median follow-up of 30 months), overall deaths in node-negative patients were similar: 24/1298 (1.8%) in the letrozole arm and 22/1301 (1.7%) in the placebo arm (hazard ratio 1.1 (CI 0.62, 1.96); *P* = 0.749).

The selected baseline characteristics for the study population are shown in Table 10, Tables 11 and 12 show disease-free and overall survival with subset analysis by receptor status, nodal status and previous chemotherapy. Figure 3 depicts the time to recurrence or relapse.

Table 10- Selected Study Population Demographics (ITT population)[1]

Baseline Status	**Letrozole N=2583**	**Placebo N=2587**
Hormone receptor status (%)		
ER+ and/or PgR+	98	98
Both unknown	2	2
Nodal status (%)		
Node negative	50	50
Node positive	46	46
Nodal status unknown	4	4
Chemotherapy	46	46

[1]Prior treatment with tamoxifen in both arms ranged from 4.5 to 6 years.

Table 11 - Disease-free and overall survival (Modified ITT population)

	Letrozole N=2582	**Placebo N=2586**	**Hazard Ratio (95% CI)**	**P-Value**
Disease-free survival (primary)				
- events (total, first events)	92 (3.6%)	155 (6.0%)	0.58 (0.45, 0.76)[1]	0.00003
- recurrence (total):	73 (2.8%)	126 (4.9%)		
in breast	9	22		
in chest wall	2	8		
in regional sites	7	4		
- distant metastases (total, first event)	55	92		
- distant metastases (total occurrences)	57	93	0.61 (0.44, 0.84)	0.003
Contralateral breast cancer (secondary)				
- including DCIS/LCIS	19	30	0.63 (0.60, 1.13) [2]	0.120
- invasive	15	25	0.60 (0.31, 1.14) [2]	0.117
Overall survival (secondary)				
- number of deaths (total)	51	62	0.82 (0.56, 1.19) [1]	0.291
Cause of death				
- Breast cancer[3]	17	23		
- Second malignancy	9	11		
- Cardiovascular death	9	13		
- Fatal stroke	2	4		
- Other, miscellaneous	13	11		
- Unknown cause	1	0		

CI = confidence interval, DCIS = ductal carcinoma in situ, LCIS = lobular carcinoma in situ. Hazard ratio of less than 1.0 indicates difference in favour of letrozole (lesser risk of recurrence); hazard ratio greater than 1.0 indicates difference in favour of placebo (higher risk of recurrence with letrozole).

[1] Analysis stratified by receptor status, nodal status and prior adjuvant chemotherapy (stratification factors as at randomization). P-value based on stratified logrank test.

[2] Odds ratio

[3] Includes 1 patient in each treatment arm with combined breast cancer and non-protocol treatment complication.

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

	Letrozole N=2582	Placebo N=2586	Hazard Ratio (95% CI)	P-Value
Disease-free survival (all events)	92	155	0.58 (0.45, 0.76)	0.00003
Receptor status				
- Receptor positive	89/2527	152/2530	0.57 (0.44, 0.75)	0.00003
Nodal status				
- Negative	25/1298	51/1301	0.48 (0.30, 0.78)	0.002
- Positive	62/1184	100/1187	0.61 (0.44, 0.83)	0.002
Chemotherapy				
- None	44/1385	75/1387	0.58 (0.40, 0.84)	0.003
- Received	48/1197	80/1199	0.59 (0.41, 0.84)	0.003
Overall survival (all events)	51	62	0.82 (0.56, 1.19)	0.291
Nodal status				
- Positive	28/1184	45/1187	0.61 (0.38, 0.97)	0.035
- Negative	19/1298	14/1301	1.36 (0.68, 2.71)	0.385

CI = confidence interval

Figure 3: Time to recurrence or relapse (Modified ITT population)

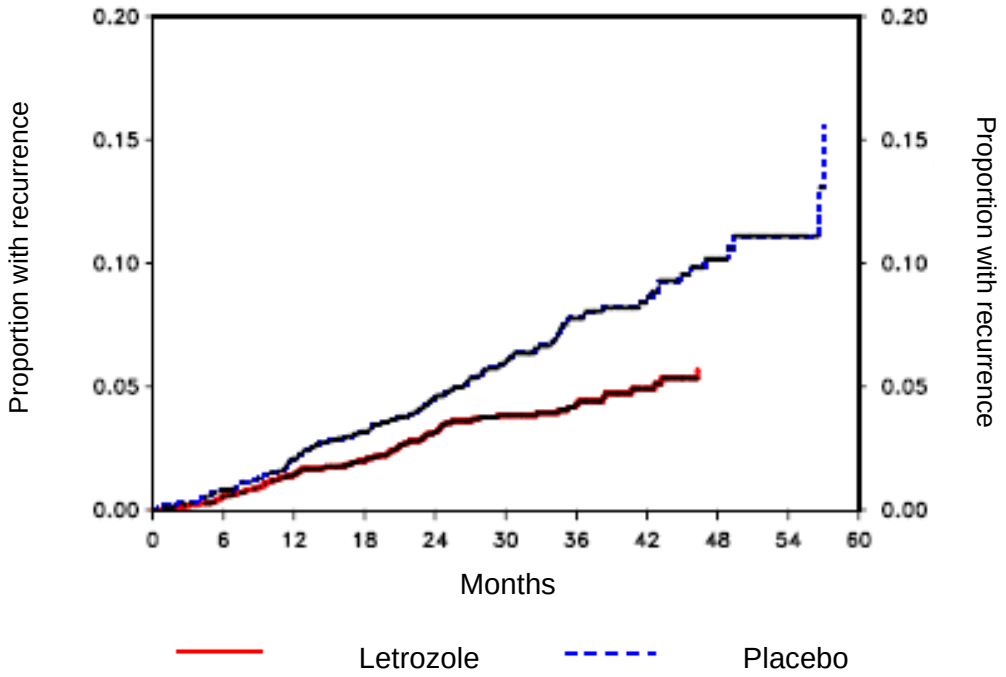
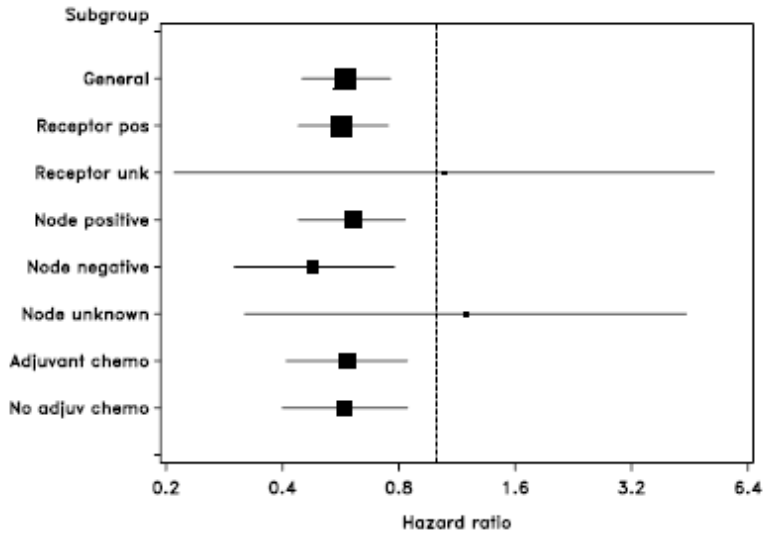


Figure 4 depicts hazard ratios (boxes) that are drawn proportional to the number of events of recurrence/relapse and to the size of the subgroups. Lines through boxes ("whiskers") denote 95% confidence intervals (CI). Dotted line denotes hazard ratio of 1.0 (no difference between treatment arms if CI crosses this line). Stratification factors with hazard ratio and 95% CI completely to left of dotted line indicate statistically significant difference in favour of letrozole.

Figure 4: Forest plot for disease-free survival (Modified ITT population)



Patient's health related quality of life was also assessed during the MA-17 study using the SF-36 Health Survey Questionnaire. The instrument has 36 questions, which yield two summary scores: physical and mental health summary measures. No clinically relevant differences were noted in physical and mental summary measures in the letrozole and placebo arms.

NOC/c **Extended Adjuvant Therapy in Early Breast Cancer, Median Treatment Duration of 47 Months, Median Follow-up of 49 Months**

Updated analyses were conducted at a median follow-up of 49 months. These results obtained after study unblinding are considered observational in nature and should therefore be interpreted with caution.

At the time of the updated analysis, 31.2% of patients in the letrozole arm and 30.4% of patients in the placebo arm had discontinued study treatment for any reason, including death, intercurrent illness, patient refusal, recurrent disease, toxicity due to protocol therapy and other reasons.

The updated efficacy analyses are based on the modified ITT population (patients analyzed according to original randomized treatment arms regardless of any subsequent switches from placebo to letrozole). After the study unblinding, 1448 (56%) of the patients in the placebo arm opted to switch to letrozole and 1138 (44%) opted to discontinue placebo and continue on no treatment. In the letrozole arm, 30% of the patients had completed 5 years of follow-up and 59% of patients had completed at least 4 years of follow-up.

The clinical interpretation of these updated analyses should take into account that patients in the randomized letrozole arm were to have started letrozole within 3 months of discontinuing adjuvant tamoxifen, as per protocol. In contrast, however, patients who switched to letrozole from placebo after study unblinding had been off adjuvant tamoxifen for a median 31 months (range 14 to 79 months).

At a median follow-up of 49 months, 6.4% of patients in the letrozole arm versus 9.1% of patients in the placebo arm experienced a breast cancer recurrence (HR 0.68; 95% CI 0.55, 0.83; *P*=0.0001). Letrozole also significantly reduced the odds of a new invasive contralateral breast cancer by 41% compared with placebo (OR 0.59; 95% CI 0.36, 0.96; *P*=0.03). There was no significant difference in distant disease-free survival or overall survival. A non-statistically significant increase in deaths (*P*=0.526) occurred in the letrozole arm in node-negative patients (53/1298 in the letrozole arm versus 48/1301 in the placebo arm). These updated results regarding node-negative patients are consistent with results at a median 30 months follow-up. (See **INDICATIONS AND CLINICAL USE** section). In contrast with the analyses conducted at 28 months median follow-up, there was no benefit for overall survival in node-positive patients treated with letrozole (HR 0.84; 95% CI 0.63, 1.11; *P*=0.219).

First-Line Therapy

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 letrozole 2.5 mg daily or tamoxifen 20 mg daily.

Time to progression (TTP) was the primary endpoint of the trial. In 907 women, letrozole was superior to tamoxifen in TTP (P<0.0001). Median TTP was 9.4 months for letrozole versus 6.0 months for tamoxifen. Letrozole 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 letrozole as compared to tamoxifen: 32% of patients in the letrozole 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 letrozole (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 letrozole. The hazard ratio comparing the subsequent risk of progression in responding patients treated with letrozole 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 letrozole, where response occurred, the subsequent risk of progression was reduced by 26% with letrozole 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 letrozole to 1% increase in the subsequent risk of progression with letrozole compared with tamoxifen in responding patients).

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

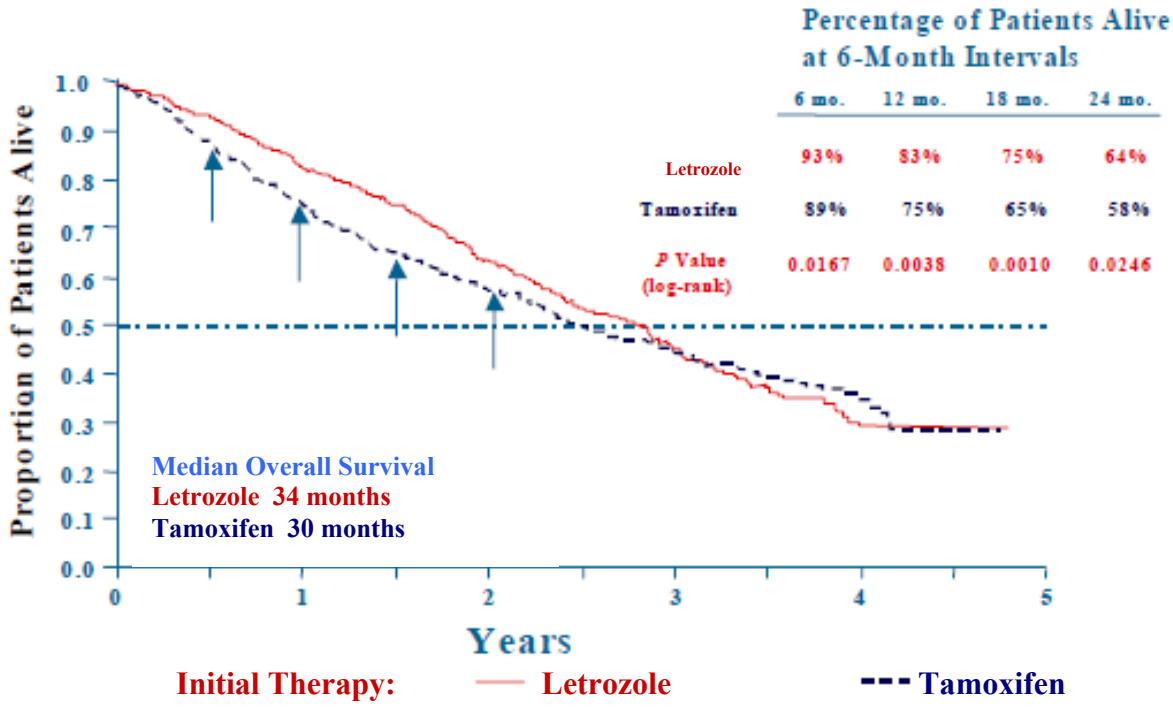
Data from this trial were further analyzed to determine the impact of prior adjuvant tamoxifen therapy on time to progression (TTP). The superiority of letrozole was observed in the subgroup of patients who received no prior adjuvant tamoxifen therapy. Patients treated with letrozole had a median TTP 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 letrozole 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 letrozole is superior to tamoxifen regardless of whether prior adjuvant therapy was initiated.

Letrozole 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 letrozole and 30 months for tamoxifen. Although this difference in overall survival was not statistically significant, there was a statistically significant early survival advantage for patients in the randomized letrozole 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 5). The total duration of endocrine therapy (time to chemotherapy) was significantly longer for letrozole (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 5
Letrozole vs. Tamoxifen Survival Analysis



In conclusion, in the above large, well controlled, double-blind, multinational, phase III clinical trial, women treated with letrozole had better results on primary and secondary endpoints (TTP, TTF objective tumour response and clinical benefit) than women treated with tamoxifen.

NOC

Second-Line Therapy

In a controlled double-blind clinical trial, the overall objective tumour response rate (complete and partial response) was 23.6% in letrozole -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 letrozole (p=0.04).

In an open-label, randomized clinical trial, survival at 2 years was 55.1% for patients treated with letrozole compared to 38.8% for patients treated with 500 mg aminoglutethimide. Treatment comparison showed a statistically significantly prolonged overall survival with letrozole (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 antitumour 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.

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 14).

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 15). 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 letrozole. However, a direct drug effect cannot be ruled out.

Table 14- 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 15 - 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.**
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**

Letrozole was evaluated for maternal toxicity as well as embryotoxic, fetotoxic and teratogenic potential in female rats following oral administration of daily doses of 0.003, 0.01 or 0.03 mg/kg on gestation days 6 through 17. Oral administration of letrozole to pregnant rats resulted in teratogenicity and maternal toxicity at 0.03 mg/kg. Embryotoxicity and fetotoxicity were seen at doses ≥0.003 mg/kg and there was an increase in the incidence of fetal malformation among the animals treated. However it is not known whether this was an indirect consequence of the pharmacological activity of letrozole (inhibition of estrogen biosynthesis) or a direct drug effect.

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 stromal tumours in mice) were secondary to the pharmacological effect of the compound. In the mouse carcinogenicity study, dermal and systemic inflammation 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 16- 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
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)

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17. FEMARA* (letrozole) 2.5 mg tablets Product Monograph by Novartis Pharmaceuticals Canada Inc. Date of Revision: September 29, 2008. Control # 123512.

PART III: CONSUMER INFORMATION

LETROZOLE, for use as adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer and as extended adjuvant treatment of hormone receptor-positive early breast cancer in postmenopausal women who have received approximately 5 years of prior standard adjuvant tamoxifen therapy, has been approved with conditions, pending the results of studies to verify its clinical benefit. For more information, patients are advised to contact their health care provider.

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products approved under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

^{Pr}LETROZOLE

(letrozole)

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

ABOUT THIS MEDICATION

What LETROZOLE is used for:

- The adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer;
- The extended adjuvant treatment of hormone receptor positive 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 in women with natural or artificially-induced postmenopausal status, who have disease progression following antiestrogen therapy.

What does LETROZOLE do:

Estrogen is a normally occurring female sex hormone that stimulates normal breast tissue and the growth of some types of breast cancer. LETROZOLE 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 LETROZOLE 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 LETROZOLE 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 LETROZOLE beyond the standard 5 years of hormone therapy is called "extended adjuvant therapy".

When it should not be used:

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

Do not take LETROZOLE if you:

- have ever had an unusual or allergic reaction to letrozole or any other ingredient in LETROZOLE;
- still have menstrual periods;
- are pregnant or breast-feeding, as LETROZOLE may harm your baby.

What the medicinal ingredient is:

Letrozole

What the nonmedicinal ingredients are:

LETROZOLE also contains the following non-medicinal ingredients needed to make the tablets: FD&C Yellow #6 aluminium lake, magnesium stearate, polyethylene glycol, polyvinyl alcohol, silicified microcrystalline cellulose, sodium starch glycollate, talc, titanium dioxide and yellow iron oxide.

What dosage forms it comes in:

LETROZOLE (letrozole) 2.5 mg tablets

LETROZOLE is supplied as film-coated tablets. The film-coated tablets are yellow and round biconvex. They are marked with "2.5" on one side and plain on the reverse side LETROZOLE is supplied in blister packs containing 28 tablets.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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

LETROZOLE 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 LETROZOLE, 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 LETROZOLE if you may become pregnant, are pregnant and/or breastfeeding. There is a potential risk of harm to you and the fetus, including risk of fetal malformations. 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.

If there is exposure to LETROZOLE 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.

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

Before you take LETROZOLE:

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. LETROZOLE may increase lipid levels.
- have or have had cardiovascular or heart disease including any of the following: heart attack, stroke or uncontrolled blood pressure. LETROZOLE may increase the risk of cardiovascular or heart diseases.

Driving a vehicle or using machinery:

LETROZOLE 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 LETROZOLE.

PROPER USE OF THIS MEDICATION

Usual dose:

The usual dosage is one tablet of LETROZOLE to be taken once daily. The tablet should be swallowed whole with a small glass of water. You can take LETROZOLE with or without food. It is best to take LETROZOLE 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 LETROZOLE, don't worry, take the missed dose as soon as you remember. However, if it is almost time for the next dose, 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

Like all medicines, LETROZOLE can have some side effects. Most side effects that have been observed were mild to moderate. 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*)

- hot flushes
- night sweat
- pain in bones and joints.

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

- headache
- rash
- dizziness
- generally feeling unwell
- 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
- bone fractures
- depression
- weight increase
- memory problems
- anxiety
- insomnia
- hair loss
- fatigue
- Increased sweating
- high level of cholesterol (hypercholesterolemia).

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

- nervous disorders (such as nervousness, irritability, drowsiness)
- reduced sense of touch (dysaesthesia)
- eye irritation
- palpitations, rapid heart rate
- raised blood pressure (hypertension)
- dry skin, itchy rash (urticaria), rapid swelling of face, lips, tongue, throat (angioedema)
- severe allergic reaction (anaphylactic reaction)
- vaginal disorders (such as bleeding, discharge or dryness)
- abdominal pain
- joint stiffness (arthritis)
- 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).

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 in all cases**		**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)		√	
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);			
- Numbness 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),		√	√
- Severe fever, chills or mouth ulcers due to infections (signs of low level of white blood cells),		√	√
- Blurred vision (sign of cataract).		√	√

This is not a complete list of side effects. For any unexpected effects while taking LETROZOLE***, 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 LETROZOLE 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: 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 0701C
Ottawa ON 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 the side effect, please contact your health care 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 by contacting Teva Canada Limited at:
1-800-268-4127 ext.5005 (English),
1-877-777-9117 (French) or
druginfo@tevacanada.com

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Teva Canada Limited
30 Novopharm court
Toronto, Ontario
Canada M1B 2K9

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