Lezra
tablets 2.5 mg

Non-steroidal aromatase inhibitor (inhibitor of oestrogen biosynthesis); antineoplastic agent.

DESCRIPTION AND COMPOSITION
Pharmaceutical form
Film-coated tablets
Yellow film-coated tablets, of round, lenticular form, with uniform appearance and intact edges.

Active substance
4,4'-[(1H-1,2,4-triazol-1-yl)-methylene]bis-benzonitrile (INN/USAN= letrozole).
Each film-coated tablet contains 2.5 mg letrozole.
Excipients
Lactose monohydrate, Maize starch, Sodium starch glycolate, Microcrystalline cellulose silicified, Magnesium stearate, Opadry II85F32410 Yellow [Polyvinyl alcohol-part. Hydrolyzed, Titanium dioxide (E171), Macrogol 3350, Talc, Iron oxide Yellow (E172)].

INDICATIONS
Letrozole is not indicated in hormone receptor negative disease.
Letrozole is indicated in:
- Adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer.
- Extended adjuvant treatment of invasive early breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy for five years.
- First-line treatment in postmenopausal women with hormone-dependent advanced breast cancer.
- Treatment of advanced breast cancer after relapse or disease progression, in women with natural or artificially induced postmenopausal endocrine status, who have previously been treated with anti-estrogens

DOSAGE AND ADMINISTRATION
Adults
The recommended dose of Lezra is 2.5 mg once daily. In the adjuvant and extended adjuvant setting, treatment with Lezra should continue for 5 years or until disease relapse/recurrence occurs, whichever comes first. In patients with metastatic disease, treatment with Lezra should continue until tumor progression is evident.

Special populations
Hepatic impairment
No dose adjustment of Lezra is required for patients with mild to moderate hepatic insufficiency (Child-Pugh score A or B). Insufficient data are available for patients with severe hepatic impairment, but patients with severe hepatic impairment (Child-Pugh score C) should be kept under close supervision (see sections WARNINGS AND PRECAUTIONS and CLINICAL PHARMACOLOGY - Pharmacokinetics).

Renal impairment
No dosage adjustment of Lezra is required for patients with renal insufficiency with creatinine clearance (CLcr) ≥10 mL/min. Insufficient data are available in cases of renal insufficiency with CLcr <10 mL/min (see sections WARNINGS AND PRECAUTIONS and CLINICAL PHARMACOLOGY - Pharmacokinetics).

Pediatrics
Lezra is not recommended for use in children and adolescents. The safety and efficacy of Lezra in children and adolescents aged up to 17 years have not been established. Limited data are available and no recommendation on a posology can be made.

Geriatric patients (65 years of age or older)
No dose adjustment is required for elderly patients.

Method of administration
Lezra should be taken orally and can be taken with or without food because food has no effect on the extent of absorption.

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

CONTRAINDICATIONS
Known hypersensitivity to the active substance or to any of the excipients.
Premenopausal endocrine status; pregnancy, lactation (see sections PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

WARNINGS AND PRECAUTIONS
Bone effects
Osteoporosis and/or bone fractures have been reported with the use of Lezra. Therefore monitoring of overall bone health is recommended during treatment (see sections ADVERSE DRUG REACTIONS and CLINICAL PHARMACOLOGY - Pharmacodynamics).

Renal impairment
Lezra has not been investigated in patients with creatinine clearance <10 mL/min. The potential risk/benefit to such patients should be carefully considered before administration of Lezra.

Hepatic impairment
In patients with severe hepatic impairment (Child-Pugh score C), systemic exposure and terminal half-life were approximately doubled compared to healthy volunteers. Such patients should therefore be kept under close supervision (see section CLINICAL PHARMACOLOGY - PHARMACOKINETICS).

Menopausal status
In patients whose menopausal status is unclear, luteinising hormone (LH), follicle-stimulating hormone (FSH) and/or estradiol levels should be measured before initiating treatment with Lezra. Only women of postmenopausal endocrine status should receive Lezra.

Fertility
The pharmacological action of letrozole is to reduce estrogen production by aromatase inhibition. In premenopausal women, the inhibition of estrogen synthesis leads to feedback increases in gonadotropin (LH, FSH) levels. Increased FSH levels in turn stimulate follicular growth, and can induce ovulation.

Interactions
Co-administration of Lezra with tamoxifen, other anti-estrogens or estrogen-containing therapies should be avoided as these substances may diminish the pharmacological action of letrozole. The mechanism of this interaction is unknown (see section INTERACTIONS).

Driving and using machines
Since fatigue and dizziness have been observed with the use of Lezra and somnolence has been reported uncommonly, caution is advised when driving or using machines.

INTERACTIONS
Letrozole is mainly metabolized in the liver and the cytochrome P450 enzymes CYP3A4 and CYP2A6 mediate the metabolic clearance of letrozole. Therefore, the systemic elimination of letrozole may be influenced by drugs known to affect the CYP3A4 and CYP2A6.

Drugs that may increase Letrozole serum concentrations
Inhibitors of CYP3A4 and CYP2A6 activities could decrease the metabolism of letrozole and thereby increase plasma concentrations of letrozole. The concomitant administration of medications that strongly inhibit these enzymes (strong CYP3A4 inhibitors: including but not limited to ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin, and telithromycin; CYP2A6 (e.g. methoxsalen) may increase exposure to letrozole. Therefore caution is recommended in patients for whom strong CYP3A4 and CYP2A6 inhibitors are administered.

Drugs that may decrease Letrozole serum concentrations
Inducers of CYP3A4 activity could increase the metabolism of letrozole and thereby decrease plasma concentrations of letrozole. The concomitant administration of medications that induce CYP3A4 (e.g. phenytoin, rifampicin, carbamazepine, phenobarbital, and St. John's Wort) may reduce exposure to letrozole. Therefore caution is recommended in patients for whom strong CYP3A4 inducers are indicated. No drug inducer is known for CYP2A6.
Co-administration of letrozole 2.5mg and tamoxifen 20 mg daily resulted in a reduction of letrozole plasma levels by 38% on average. There is limited clinical experience to date on the use of letrozole 2.5mg in combination with other anti-cancer agents other than tamoxifen.

Drugs that may have their systemic serum concentrations altered by Letrozole
In vitro, letrozole inhibits the cytochrome P450 isoenzymes CYP2A6 and, moderately, CYP2C19, but the clinical relevance is unknown. Caution is therefore indicated when giving letrozole concomitantly with medicinal products whose elimination is mainly dependent on CYP2C19 and whose therapeutic index is narrow (e.g. phenytoin, clopidrogel). No substrate with a narrow therapeutic index is known for CYP2A6.

Clinical interaction studies with cimetidine (a known non-specific inhibitor of CYP2C19 and CYP3A4 and warfarin (sensitive substrate for CYP2C9 with a narrow therapeutic window and commonly used as co-medication in the target population of letrozole) indicated that the coadministration of Lezra with these drugs does not result in clinically significant drug interactions.

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

Pregnancy, lactation, females and males of reproductive potential

Pregnancy
Letrozole is contraindicated during pregnancy (see section CONTRAINDICATIONS). There are post-marketing reports of spontaneous abortions and congenital anomalies in infants of mothers who took letrozole (see section WARNINGS AND PRECAUTIONS) during pregnancy.

Isolated cases of birth defects (labial fusion, ambiguous genitalia) have been reported in infants born to pregnant women exposed to letrozole (see also section NON-CLINICAL SAFETY DATA).

Breast-feeding
Lezra is contraindicated during lactation (see section CONTRAINDICATIONS).

Females and males of reproductive potential
The physician needs to discuss the necessity of adequate contraception with women who have the potential to become pregnant including women who are perimenopausal or who recently became postmenopausal, until their postmenopausal status is fully established.

ADVERSE DRUG REACTIONS
Summary of the safety profile
Lezra was generally well tolerated across all studies as first-line and second-line treatment for advanced breast cancer, as adjuvant treatment of early breast cancer and as extended adjuvant treatment in women who have received prior standard tamoxifen therapy. Approximately one third of the patients treated with Lezra in the metastatic and neoadjuvant settings, approximately 75% of the patients in the adjuvant setting (both Lezra and tamoxifen arms, at a median treatment duration of 60 months), and approximately 80% of the patients in the extended adjuvant setting (both Lezra and placebo arms, at a median treatment duration of 60 months) experienced adverse reactions. Generally, the observed adverse reactions are mainly mild or moderate in nature, and most are associated with oestrogen deprivation.

The most frequently reported adverse reactions in the clinical studies were hot flushes, arthralgia, nausea and fatigue. Many adverse reactions can be attributed to the normal pharmacological consequences of oestrogen deprivation (e.g. hot flushes, alopecia and vaginal bleeding). The following adverse drug reactions, listed in Table 1, were reported from clinical studies and from post marketing experience with Letrozole tablets 2.5mg.

Tabulated summary of adverse drug reactions from clinical trials and from post marketing experience with Letrozole

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: very common ≥10%, common ≥1% to <10%, uncommon ≥0.1% to <1%, rare ≥0.01% to <0.1%, very rare <0.01%, not known (cannot be estimated from the available data)

Table 1 Adverse drug reactions

Infections and infestations	
Uncommon	Urinary tract infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Uncommon	Tumour pain[1]
Blood and the lymphatic system disorders	
Uncommon	Leukopenia
Immune system disorders	
Not known	Anaphylactic reaction
Metabolism and nutrition disorders	
Very common	Hypercholesterolemia
Common	Decreased appetite, increased appetite
Psychiatric disorders	
Common	Depression
Uncommon	Anxiety (including nervousness), irritability
Nervous system disorders	
Common	Headache, dizziness, vertigo
Uncommon	Somnolence, insomnia, memory impairment, dysaesthesia (including paresthesia, hypoesthesia), dysgeusia, cerebrovascular accident, carpal tunnel syndrome
Eye disorders	
Uncommon	Cataract, eye irritation, blurred vision
Cardiac disorders	
Common	Palpitations
Uncommon	Tachycardia, ischemic cardiac events (including new or worsening angina, angina requiring surgery, myocardial infarction and myocardial ischemia)
Vascular disorders	
Very common	Hot flushes
Common	Hypertension
Uncommon	Thrombophlebitis (including superficial and deep vein thrombophlebitis)
Rare	Pulmonary embolism, arterial thrombosis, cerebrovascular infarction
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, cough
Gastrointestinal disorders	
Common	Nausea, vomiting, dyspepsia, constipation, diarrhoea, abdominal pain
Uncommon	Stomatitis, dry mouth
Hepato-biliary disorders	
Uncommon	Increased hepatic enzymes, hyperbilirubinaemia, jaundice
Very rare	Hepatitis
Skin and subcutaneous tissue disorders	
Very common	Hyperhidrosis
Common	Alopecia, dry skin, rash (including erythematous, maculopapular, psoriaform, and vesicular rash)
Uncommon	Pruritus, urticaria
Not known	Angioedema, toxic epidermal necrolysis, erythema multiforme
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia
Common	Myalgia, bone pain, osteoporosis, bone fractures, arthritis, back pain
Not known	Trigger finger
Renal and urinary disorders	
Uncommon	Pollakiuria
Reproductive system and breast disorders	
Common	Vaginal bleeding
Uncommon	Vaginal discharge, vaginal dryness, breast pain
General disorders and administration site conditions	
Very common	Fatigue (including asthenia, malaise)
Common	Peripheral oedema, chest pain
Uncommon	General edema, pyrexia, mucosal dryness, thirst
Investigations	
Common	Weight increase
Uncommon	Weight loss
Injury, poisoning and procedural complications	
Common[2]	Fall[3]

[1] Adverse drug reactions reported only in the metastatic setting
[2] Frequency determined based on FACE Study data
[3] In some cases fall was reported as a consequence of other adverse events such as dizziness and vertigo

Description of selected adverse drug reactions
Cardiac adverse reactions
In the adjuvant setting, in addition to the data presented in Table 6, the following adverse events were reported for Letrozole tablets and tamoxifen, respectively (median treatment duration of 5 years): angina requiring surgery (1.0% vs. 1.0%); cardiac failure (1.1% vs. 0.6%); hypertension (5.6% vs. 5.7%); cerebrovascular accident/transient ischaemic attack (2.1% vs. 1.9%).
In the extended adjuvant setting for Letrozole tablets (median duration of treatment 5 years) and placebo (median duration of treatment 3 years), respectively: angina requiring surgery (0.8% vs. 0.6%); new or worsening angina (1.4% vs. 1.0%); myocardial infarction (1.0% vs. 0.7%); thromboembolic event* (0.9% vs. 0.3%); stroke/transient ischaemic attack* (1.5% vs. 0.8%) were reported.
Events marked * were statistically significantly different in the two treatment arms.

Skeletal adverse reactions
For skeletal safety data from the adjuvant setting, please refer to Table 6.
In the extended adjuvant setting, significantly more patients treated with Letrozole tablets experienced bone fractures or osteoporosis (bone fractures, 10.4% and osteoporosis, 12.2%) than patients in the placebo arm (5.8% and 6.4%, respectively). Median duration of treatment was 5 years for Letrozole tablets, compared with 3 years for placebo.

OVERDOSAGE
Isolated cases of overdosage with Lezra have been reported.
No specific treatment for overdosage is known; treatment should be symptomatic and supportive.

CLINICAL PHARMACOLOGY
Mechanism of action (MOA)
The elimination of estrogen-mediated stimulatory effects is a prerequisite for tumor response in cases where the growth of tumor tissue depends on the presence of estrogens. In postmenopausal women, estrogens are mainly derived 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 cancer tissue itself can therefore be achieved by specifically inhibiting the aromatase enzyme.
Letrozole is a non-steroidal aromatase inhibitor. It inhibits the aromatase enzyme by competitively binding to the hem of the cytochrome P450 subunit of the enzyme, resulting in a reduction of estrogen biosynthesis in all tissues.

PHARMACODYNAMICS
Pharmacodynamic effects
In healthy postmenopausal women, single doses of 0.1 mg, 0.5 mg and 2.5 mg letrozole suppress serum oestrone and oestradiol by 75 to 78 % and 78 % from baseline, respectively. Maximum suppression is achieved in 48 to 78 hours.
In postmenopausal patients with advanced breast cancer, daily doses of 0.1 to 5 mg suppress plasma concentration of oestradiol, oestrone, and oestrone sulphate by 75 to 95 % from baseline in all patients treated. With doses of 0.5 mg and higher, many values of oestrone and oestrone sulphate are below the limit of detection in the assays, indicating that higher oestrogen suppression is achieved with these doses. Oestrogen suppression was maintained throughout treatment in all these patients. Letrozole is highly specific in inhibiting aromatase activity. Impairment of adrenal steroidogenesis has not been observed. No clinically relevant changes were found in the plasma concentrations of cortisol, aldosterone, 11-deoxycortisol, 17-hydroxy-progesterone, and ACTH, or in plasma renin activity among postmenopausal patients treated with a daily dose of letrozole 0.1 to 5 mg. The ACTH stimulation test performed after 6 and 12 weeks of treatment with daily doses of 0.1 mg, 0.25 mg, 0.5 mg, 1 mg, 2.5 mg, and 5 mg did not indicate any attenuation of aldosterone or cortisol production. Thus, glucocorticoid and mineralocorticoid supplementation is not necessary.
No changes were noted in plasma concentrations of androgens (androstenedione and testosterone) among healthy postmenopausal women after 0.1 mg, 0.5 mg, and 2.5 mg single doses of letrozole or in plasma concentrations of androstenedione among postmenopausal patients treated with daily doses of 0.1 to 5 mg, indicating that the blockade of oestrogen biosynthesis does not lead to accumulation of androgenic precursors. Plasma levels of LH and FSH are not affected by letrozole in patients, nor is thyroid function as evaluated by TSH, T4 and T3 uptake.

PHARMACOKINETICS
Absorption
Letrozole is rapidly and completely absorbed from the gastrointestinal tract (mean absolute bioavailability: 99.9%). Food slightly decreases the rate of absorption (median t_{max}: 1 hour fasted versus 2 hours fed; and mean C_{max}: 129 ± 20.3 nmol/L fasted versus 98.7 ± 18.6 nmol/L fed), but the extent of absorption (AUC) is not changed. The minor effect on the absorption rate is not considered to be of clinical relevance, and therefore letrozole may be taken without regard to meal times.

Distribution
Plasma protein binding of letrozole is approximately 60%, mainly to albumin (55%). The concentration of letrozole 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. Letrozole is rapidly and extensively distributed to tissues. Its apparent volume of distribution at steady state is about 1.87 ± 0.47 L/kg.

Biotransformation/metabolism
Metabolic clearance to a pharmacologically inactive carbinol metabolite is the major elimination pathway of letrozole (CLm= 2.1 L/h), but 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 faecal 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 faeces. 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.

Elimination
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 the steady-state values predicted from the concentrations measured after a single dose, indicating a slight non-linearity in the pharmacokinetics of letrozole upon daily administration of 2.5 mg. Since steady-state levels are maintained over time, it can be concluded that no continuous accumulation of letrozole occurs.

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

Special populations
Elderly
Age had no effect on the pharmacokinetics of letrozole.

Renal Impairment
In a study involving volunteers with varying degrees of renal function (24-hour creatinine clearance 9 to 116 mL/min), no effect on the pharmacokinetics systemic exposure of letrozole was found after a single dose of 2.5 mg. Therefore, no dose adjustment is required for patients with renal impairment (CLcr ≥10 mL/min). Little information is available in patients with severe impairment of renal function (CLcr <10 mL/min.

Hepatic Impairment
In a similar study involving subjects with varying degrees of hepatic function, the mean AUC values of the volunteers with moderate hepatic impairment (Child-Pugh score B) was 37% higher than in normal subjects, but still within the range seen in subjects without impaired function. In a study comparing the pharmacokinetics of letrozole after a single oral dose in eight subjects with liver cirrhosis and severe hepatic impairment (Child-Pugh score C) to those in healthy volunteers (n=8), AUC and $t_{1/2}$ 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. However, since in patients dosed at 5 or 10 mg/day no increase in toxicity was observed, a dose reduction in patients with severe hepatic impairment appears not to be warranted, although such patients should be kept under close supervision. In addition, in two well-controlled studies involving 359 patients with advanced breast cancer, no effect of renal impairment (calculated creatinine clearance: 20 to 50 mL/min) or hepatic dysfunction was found on the letrozole concentration.

CLINICAL STUDIES

Adjuvant treatment

Study BIG 1-98 (CFEM345D019)

BIG 1-98 was a multicenter, double-blind study in which over 8,000 postmenopausal women with hormone receptor-positive early breast cancer were randomized to one of the following treatments: A. tamoxifen for 5 years; B. Letrozole tablets for 5 years; C. tamoxifen for 2 years followed by Letrozole tablets for 3 years; D. Letrozole tablets for 2 years followed by tamoxifen for 3 years.

The primary endpoint was disease-free survival (DFS); secondary efficacy endpoints were time to distant metastasis (TDM), distant disease-free survival (DDFS), overall survival (OS), systemic disease-free survival (SDFS), invasive contralateral breast cancer and time to breast cancer recurrence.

Efficacy results at a median follow-up of 26 and 60 months

Data in Table 2 reflect the results of the Primary Core Analysis (PCA) based on data from the monotherapy arms (A and B) and from the two switching arms (C and D) at a median treatment duration of 24 months and a median follow-up of 26 months and at a median treatment duration of 32 months and a median follow-up of 60 months.

The 5-year DFS rates were 84% for Lezra and 81.4% for tamoxifen.

Table 2 Primary Core Analysis: Disease-free and overall survival, at a median follow-up of 26 months and at median follow-up of 60 months (ITT population)

	Primary Core Analysis					
	Median follow-up 26 months			Median follow-up 60 months		
	Letrozole N=4003	Tamoxifen N=4007	HR[1] (95% CI) *P*	Letrozole N=4003	Tamoxifen N=4007	HR[1] (95% CI) *P*
Disease-free survival event[2]	351	428	0.81 (0.70, 0.93) 0.003	585	664	0.86 (0.77, 0.96) 0.008
Overall survival[3]	166	192	0.86 (0.70, 1.06)	330	374	0.87 (0.75, 1.01)

HR = Hazard ratio; CI = Confidence interval

[1] Log rank test, stratified by randomisation option and use of chemotherapy (yes/no)

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

[3] Number of deaths

Results at a median follow-up of 96 months (monotherapy arms only)

The Monotherapy Arms Analysis (MAA) long-term update of the efficacy of Letrozole tablets monotherapy compared to tamoxifen monotherapy (median duration of adjuvant treatment: 5 years) is presented in Table 3.

Table 3 Monotherapy Arms Analysis: Disease-free and overall survival at a median follow-up of 96 months (ITT population)

	Letrozole N=2463	Tamoxifen N=2459	Hazard Ratio[1] (95% CI)	*P Value*
Disease-free survival events[2]	626	698	0.87 (0.78, 0.97)	0.01
Time to distant metastasis	301	342	0.86 (0.74, 1.01)	0.06
Overall survival - [3]	393	436	0.89 (0.77, 1.02)	0.08
Censored analysis of DFS[4]	626	649	0.83 (0.74, 0.92)	
Censored analysis of OS[4]	393	419	0.81 (0.70, 0.93)	

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

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

[3] Number of deaths

[4] Observations in the tamoxifen arm censored at the date of selectively switching to letrozole after tamoxifen arm was unblinded

Sequential Treatment Analysis (STA)

The Sequential Treatments Analysis (STA) addresses the second primary question of BIG 1-98, namely whether sequencing of tamoxifen and letrozole would be superior to monotherapy. There were no significant differences in DFS, OS, SDFS, or DDFS from switch with respect to monotherapy (Table 4).

Table 4 Sequential treatments analysis of disease-free survival with letrozole as initial endocrine agent (STA switch population)

	N	Number of events[1]	Hazard ratio[2]	(97.5% confidence interval)	Cox model *P*-value
[Letrozole→] Tamoxifen	1,460	254	1.03	(0.84, 1.26)	0.72
Letrozole	1,463	249			

[1] Protocol definition, including second non-breast primary malignancies, after switch / beyond two years

[2] Adjusted by chemotherapy use

There were no significant differences in DFS, OS, SDFS or DDFS in any of the STA from randomization pairwise comparisons (Table 5).

Table 5 Sequential Treatments Analyses from randomization (STA-R) of disease-free survival (ITT STA-R population)

	Letrozole→ Tamoxifen	Letrozole
Number of patients	1,540	1,546
Number of patients with DFS events (protocol definition)	330	319
Hazard ratio1 (99% CI)	1.04 (0.85, 1.27)	
	Letrozole→ Tamoxifen	**Tamoxifen[2]**
Number of patients	1,540	1,548
Number of patients with DFS events (protocol definition)	330	353
Hazard ratio1 (99% CI)	0.92 (0.75, 1.12)	

[1] Adjusted by chemotherapy use (yes/no)

[2] 626 (40%) patients selectively crossed to letrozole after tamoxifen arm unblinded in 2005

The following tables 6 and table 7 provide information on significant differences in letrozole versus tamoxifen monotherapy and in the letrozole-tamoxifen sequential treatment therapy:

Table 6 Adjuvant Letrozole tablets monotherapy versus tamoxifen monotherapy - adverse events with significant differences

	Letrozole tablets N=2448		Tamoxifen N=2447	
	During treatment (median 5 years)	Any time after randomization (median 96 months)	During treatment (median 5 years)	Any time after randomization (median 96 months)
Bone fracture	10.2%	14.7%	7.2%	11.4%
Osteoporosis	5.1%	5.1%	2.7%	2.7%
Thromboembolic events	2.1%	3.2%	3.6%	4.6%
Myocardial infarction	1.0%	1.7%	0.5%	1.1%
Endometrial hyperplasia / endometrial cancer	0.2%	0.4%	2.3%	2.9%

Note: Median duration of treatment 60 months. Reporting period includes treatment period plus 30 days after stopping treatment.

"Any time after randomization" includes the follow-up period after completion or cessation of study treatment

Table 7 Sequential treatment versus Letrozole monotherapy-adverse events with significant differences

	Letrozole tablets mono-therapy 5 years	Letrozole tablets >Tamoxifen 2 years + 3 years	Tamoxifen > Letrozole 2tablets years + 3 years
	N=1535	N=1527	N=1541
Bone fractures	10.0%	7.7%*	9.7%
Endometrial proliferative disorders	0.7%	3.4%**	1.7%**
Hypercholesterolemia	52.5%	44.2%*	40.8%*
Hot flushes	37.6%	41.7%**	43.9%**
Vaginal bleeding	6.3%	9.6%**	12.7%**

** Significantly less than with Letrozole tablets monotherapy*

***Significantly more than with Letrozole tablet monotherapy*

Note : Reporting period is during treatment or within 30 days of stopping treatment

Study CFEM345D2407

Study D2407 was an open-label, randomized, multicenter post authorization safety study designed to compare the effects of adjuvant treatment with Letrozole and tamoxifen on bone mineral density (BMD) and serum lipid profiles. A total of 263 patients were assigned either Letrozole for 5 years or tamoxifen for 2 years followed by letrozole for 3 years.

At 24 months there was a statistically significant difference in the primary end-point; the lumbar spine BMD (L2-L4) showed a median decrease of 4.1% for letrozole compared to a median increase of 0.3% for tamoxifen.

No patient with a normal BMD at baseline became osteoporotic during 5 years of treatment and only 1 patient with osteopenia at baseline (T score of -1.9) developed osteoporosis during the treatment period (assessment by central review).

The results for total hip BMD were similar to those for lumbar spine but less pronounced.

Although treatment differences at the end of 5 years were attenuated such that there was no statistically significant difference between treatments in the protocol-defined clinically relevant BMD-related changes overall, there remained substantial differences in the effects of the two treatments on BMD and skeletal events. In patients with a normal T-score at baseline, significantly more patients in the letrozole arm than in the sequential treatment arm had reductions of at least 6% in lumbar spine BMD within 1 year or cumulative reductions of at least 8% over the entire treatment period. Although there was no significant difference overall between treatment arms in clinical fractures, three-quarters of the fractures in the sequential treatment arm occurred after the switch to letrozole.

Both clinical fractures and impending fractures, however, tended to occur in patients whose skeletal status was compromised – i.e. patients with lower BMD T-scores at baseline, and patients with a history of fractures.

Total cholesterol levels (fasting) decreased by a median 16% in the tamoxifen arm at 6 months, and remained so for the duration of tamoxifen therapy. In the letrozole arm, total cholesterol levels were relatively stable throughout treatment. LDL cholesterol levels decreased in the tamoxifen arm but remained stable in the letrozole arm. Consequently, there were statistically significant differences in favour of tamoxifen in total cholesterol, LDL cholesterol and HDL: LDL ratio over the first 2 years of the study. There were no significant differences between treatments in triglycerides.

Extended adjuvant treatment

Study MA-17 (CFEM345MA17)

In a multicenter, double-blind, randomized, placebo-controlled study (MA-17), over 5,100 postmenopausal women with receptor-positive or unknown primary breast cancer who had completed adjuvant treatment with tamoxifen (4.5 to 6 years) were randomized to either letrozole or placebo for 5 years.

The primary endpoint was disease-free survival, defined as the interval between randomization and the earliest occurrence of loco-regional recurrence, distant metastasis, or contralateral breast cancer.

The first planned interim analysis at a median follow-up of around 28 months (25% of patients being followed up for at least 38 months), showed that letrozole significantly reduced the risk of breast cancer recurrence by 42% compared with placebo (HR 0.58; 95% CI 0.45, 0.76; *P*=0.00003). The benefit in favor of letrozole was observed regardless of nodal status. There was no significant difference in overall survival: (letrozole 51 deaths; placebo 62; HR 0.82; 95% CI 0.56, 1.19). Consequently, after the first interim analysis the study was unblinded and continued in an open-label fashion and patients in the placebo arm were allowed to switch to letrozole for up to 5 years. Over 60% of eligible patients (disease-free at unblinding) opted to switch to letrozole. The final analysis included 1,551 women who switched from placebo to letrozole at a median of 31 months (range 12 to 106 months) after completion of tamoxifen adjuvant therapy. Median duration for letrozole after switch was 40 months.

The final analysis conducted at a median follow-up of 62 months confirmed the significant reduction in the risk of breast cancer recurrence with letrozole

Table 8 Disease-free and overall survival (Modified ITT population)

	Median follow-up 28 months			Median follow-up 62 months		
	Letrozole N=2582	Placebo N=2586	HR (95% CI)[1] *P value*	Letrozole N=2582	Placebo N=2586	HR (95% CI)[1] *P value*
Disease-free survival[3]						
Events	92 (3.6%)	155 (6.0%)	0.58 (0.45, 0.76) 0.00003	209 (8.1%)	286 (11.1%)	0.75 (0.63, 0.89)
4-year DFS rate	94.4%	89.8%		94.4%	91.4%	
Disease-free survival[3], including deaths from any cause						
Events	122 (4.7%)	193 (7.5%)	0.62 (0.49, 0.78)	344 (13.3%)	402 (15.5%)	0.89 (0.77, 1.03)
5 year DFS rate	90.5%	80.8%		88.8%	86.7%	
Distant metastases						
Events	57 (2.2%)	93 (3.6%)	0.61 (0.44, 0.84)	142 (5.5%)	169 (6.5%)	0.88 (0.70, 1.10)
Overall survival						
Deaths	51 (2.0%)	62 (2.4%)	0.82 (0.56, 1.19)	236 (9.1%)	232 (9.0%)	1.13 (0.95, 1.36)
Deaths[4]	- -	- -	- -	235[5] (9.1%)	170[5] (6.6%)	0.78 (0.64, 0.96)

HR = Hazard ratio; CI = Confidence Interval

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

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

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

[4] Exploratory analysis, censoring follow-up times at the date of switch (if it occurred) in the placebo arm.

[5] Median follow-up 62 months.

[6] Median follow-up until switch (if it occurred) 37 months.

In the MA-17 bone substudy in which concomitant calcium and vitamin D were given, greater decreases in BMD compared to baseline occurred with Letrozole tablets compared with placebo. The only statistically significant difference occurred at 2 years and was in total hip BMD (letrozole median decrease of 3.8% vs placebo median decrease of 2.0%).

In the MA-17 lipid substudy there were no significant differences between letrozole and placebo in total cholesterol or in any lipid fraction. In the updated quality of life substudy there were no significant differences between treatments in physical component summary score or mental component summary score, or in any domain score in the SF-36 scale. In the MENQOL scale, significantly more women in the Letrozole arm than in the placebo arm were most bothered (generally in the first year of treatment) by those symptoms deriving from estrogen deprivation - hot flushes and vaginal dryness. The symptom that bothered most patients in both treatment arms was aching muscles, with a statistically significant difference in favor of placebo.

Neoadjuvant treatment

Study CFEM245E P024

A double blind trial (P024) was conducted in 337 postmenopausal breast cancer patients randomly allocated either Letrozole tablets 2.5 mg for 4 months or tamoxifen for 4 months. At baseline all patients had tumors stage T2-T4c, N0-2, M0, ER and/or PgR positive and none of the patients would have qualified for breast-conserving surgery. Based on clinical assessment there were 55% objective responses in the Letrozole tablets arm versus 36% for the tamoxifen arm (*P*<0.001). This finding was consistently confirmed by ultrasound (Letrozole tablets 35% vs tamoxifen 25%, *P*=0.04) and mammography (Letrozole tablets 34% vs tamoxifen 16%, *P*<0.001). In total 45% of patients in the Letrozole tablets group versus 35% of patients in the tamoxifen group (*P*=0.02) underwent breast-conserving therapy). During the 4-month pre-operative treatment period, 12% of patients treated with Letrozole tablets and 17% of patients treated with tamoxifen had disease progression on clinical assessment.

First-line treatment

Study CFEM345C P025

One controlled double-blind trial was conducted comparing letrozole 2.5 mg to tamoxifen 20 mg as first-line therapy in postmenopausal women with advanced breast cancer. In 907 women, letrozole was superior to tamoxifen in time to progression (primary endpoint) and in overall objective response, time to treatment failure and clinical benefit. The results are summarized in Table 9:

Table 9 Results at a median follow-up of 32 months

Variable	**Statistic**	**Letrozole tablets N=453**	**Tamoxifen N=454**
Time to progression	**Median**	**9.4 months**	**6.0 months**
	(95% CI for median)	(8.9, 11.6 months)	(5.4, 6.3 months)
	Hazard ratio (HR)	0.72	
	(95% CI for HR)	(0.62, 0.83)	
		P<0.0001	
Objective response rate (ORR)	**CR+PR**	**145 (32%)**	**95 (21%)**
	(95% CI for rate)	(28, 36%)	(17, 25%)
	Odds ratio	1.78	
	(95% CI for odds ratio)	(1.32, 2.40)	
		P=0.0002	

Time to progression was significantly longer, and response rate significantly higher for letrozole irrespective of whether adjuvant anti-estrogen therapy had been given or not. Time to progression was significantly longer for letrozole irrespective of dominant site of disease. Median time to progression was 12.1 months for Letrozole tablets and 6.4 months for tamoxifen in patients with soft tissue disease only and median 8.3 months for Letrozole tablets and 4.6 months for tamoxifen in patients with visceral metastases.

Study design allowed patients to cross over upon progression to the other therapy or discontinue from the study. Approximately 50% of patients crossed over to the opposite treatment arm and crossover was virtually completed by 36 months. The median time to crossover was 17 months (letrozole tablets to tamoxifen) and 13 months (tamoxifen to letrozole tablets).

Letrozole tablets treatment in the first-line therapy of advanced breast cancer resulted in a median overall survival of 34 months compared with 30 months for tamoxifen (log rank test P=0.53, not significant). The absence of an advantage for letrozole tablets on overall survival could be explained by the crossover design of the study.

Second-line treatment

Two well-controlled clinical trials were conducted comparing two letrozole doses (0.5 mg and 2.5 mg) to megestrol acetate and to aminoglutethimide, respectively, in postmenopausal women with advanced breast cancer previously treated with anti-estrogens.

Study AR/BC2

Statistically significant differences were observed in favour of letrozole 2.5 mg compared to megestrol acetate in overall objective tumor response rate (24% vs 16%, P=0.04), and in time to treatment failure (P=0.04). Overall survival and time to progression was not significantly different between the 2 arms (P=0.2 and P=0.07, respectively).

Study AR/BC3

Letrozole 2.5 mg was statistically superior to aminoglutethimide 250 mg bd for time to progression (P=0.008), time to treatment failure (P=0.003) and overall survival (P=0.002). In this study, the response rate was not significantly different between letrozole 2.5 mg and aminoglutethimide (P=0.06).

Male breast cancer

Use of letrozole tablets in men with breast cancer has not been studied.

NON-CLINICAL SAFETY DATA

In a variety of preclinical safety studies conducted in standard animal species, there was no evidence of systemic or target organ toxicity. Letrozole tablets showed a low degree of acute toxicity in rodents exposed to up to 2000 mg/kg. In dogs, Letrozole tablets caused signs of moderate toxicity at 100 mg/kg.

In repeated-dose toxicity studies in rats and dogs up to 12 months, the main findings observed can be attributed to the pharmacological action of the compound.

Oral administration of letrozole to female rats resulted in decreases in mating and pregnancy ratios and increases in pre-implantation loss. Effects on the liver (increased weight, hepatocellular hypertrophy, fatty changes) were observed, mainly at high dose levels. 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 hepatin enzyme-inducing properties of letrozole tablets. However, a direct drug effect cannot be ruled out.

The pharmacological effects of letrozole resulted in skeletal, neuroendocrine and reproductive findings in a juvenile rat study. Bone growth and maturation were decreased from the lowest dose (0.003 mg/kg/day) in males and increased from the lowest dose (0.003 mg/kg) in females. Bone Mineral Density (BMD) was also decreased at that dose in females. In the same study, decreased fertility at all doses was accompanied by hypertrophy of the hypophysis, testicular changes which included a degeneration of the seminiferous tubular epithelium and atrophy of the female reproductive tract. With the exception of bone size in females and morphological changes in the testes, all effects were at least partially reversible.

In a 104-week mouse carcinogenicity study, dermal and systemic inflammation occurred, particularly at the highest dose of 60 mg/kg, leading to increased mortality at this dose level.

Both *in vitro* and *in vivo* investigations on letrozole's mutagenic potential revealed no indication of any genotoxicity.

In a 104-week rat carcinogenicity study, no treatment-related tumours were noted in male rats. In female rats, a reduced incidence of benign and malignant mammary tumours at all the doses of letrozole was found.

In a 104-week mouse carcinogenicity study, no treatment-related tumors were noted in male mice. In female mice, a generally dose-related increase in the incidence of benign ovarian granulosa theca cell tumors was observed at all doses of letrozole tested. These tumors were considered to be related to the pharmacological inhibition of estrogen synthesis and may be due to increased LH resulting from the decrease in circulating estrogen.

Oral administration of letrozole to gravid Sprague-Dawley rats resulted in a slight increase in the incidence of fetal malformation (domed head and fused centrum/vertebrae) among the animals treated. However, it was not possible to show whether this was an indirect consequence of the pharmacological properties (inhibition of oestrogen biosynthesis), or a direct effect of letrozole in its own right (see sections CONTRAINDICATIONS and PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

Preclinical observations were confined to those associated with the recognised pharmacological action, which is the only safety concern for human use derived from animal studies.

INCOMPATIBILITIES

Not applicable.

STORAGE

Do not store above 30°C and do protect from moisture.

Lezra tablets 2.5mg must not be used after the date marked "EXP" on the pack.

Lezra tablets 2.5mg must be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING

No specific instructions for use/handling.

Pack Size

Blister pack of 30's Tablets.

Manufacturer:

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