Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT:

Fempro (Letrozole Tablets USP 2.5 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each film coated tablet contains:

Letrozole USP… .....2.5 mg

Colours: Yellow Oxide of iron & Titanium Dioxide

Excipients with known effects: Lactose.

3. PHARMACEUTICAL FORM:

Film coated tablets

Description: Yellow circular, biconvex, film coated tablets plain on both sides.

4. CLINICAL PARTICULARS:

4.1. Therapeutic indications:

For the treatment of postmenopausal women with hormone receptor positive breast cancer (see section 5.1).

The safety and efficacy of neoadjuvant use of letrozole has not been established. Letrozoleis not indicated in hormone receptor negative disease.

4.2. Posology and method of administration:

Adults

The recommended dose of letrozole is one 2.5 mg tablet daily.

In the adjuvant setting, treatment should continue for 5 years or until tumour relapse occurs, whichever comes first.

In the extended adjuvant setting, the optimal treatment duration with letrozole is not known. The planned duration of treatment in the pivotal study was 5 years. However, at the time of the analysis, the median duration of treatment was 24 months, 25% of patients were treated for at least three years and less than 1% of patients were treated for the planned 5 years. The

median duration of follow up was 28 months. Treatment should be discontinued at tumour relapse.

In the adjuvant setting the median duration of treatment was 25 months, 73% of the patients were treated for more than 2 years, 22% of the patients for more than 4 years. The median duration of follow up was 30 months (the efficacy data mentioned in “section 5.1” are based on the Primary Core Analysis with a median duration of follow up of 26 months).

In patients with metastatic disease, treatment with letrozole should continue until tumour progression is evident.

Elderly patients

No dose adjustment is required.

Patients with hepatic/ renal impairment

No dosage adjustment of letrozole is required for patients with mild renal impairment (creatinine clearance ≥ 30 mL/min). Insufficient data are available to justify dose advice in cases of renal insufficiency with creatinine clearance less than 30 mL/min. Insufficient data are available to justify dose advice in patients with severe hepatic insufficiency. Patients with severe hepatic impairment (Child-Pugh score C) should be kept under close supervision (see sections 4.4 and 5.2).

Children

Letrozole is not recommended for use in children and adolescents. The safety and efficacy of letrozole in children and adolescents aged up to 18 years have not been established. Limited data are available and no recommendation on a posology can be made.

Method of administration

Letrozole should be taken orally. A 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.

4.3. Contraindications:

- Hypersensitivity to the active substance or to any of the excipients
- Premenopausal endocrine status; pregnancy, lactation (see section 4.4)

4.4. Special warnings and precautions for use:

Use with Caution in the Following Circumstances

Renal impairment:

Letrozole has not been investigated in patients with creatinine clearance < 10 mL/min nor in a sufficient number of patients with a creatinine clearance less than 30 mL/min. The potential risk/benefit to such patients should be carefully considered before administration of letrozole. As letrozole is weakly bound to plasma proteins (see section 5.2), it is anticipated that it could be removed from circulation by dialysis. Similar caution should be exercised in patients with severe hepatic insufficiency.

Hepatic impairment:

In patients with severe hepatic cirrhosis (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 5.2).

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 letrozole. Only women of postmenopausal endocrine status should receive letrozole.

Interactions

Co-administration of letrozole 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.

Bone effects

Osteoporosis and/or bone fractures have been reported with the use of letrozole. Therefore monitoring of overall bone health is recommended during treatment (see sections 4.8 and 5.1)

Lactose intolerance

Fempro contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5. Interaction with other medicinal products and other forms of interaction

To date, there are minimal data on the interaction between letrozole and other drugs.

Additionally, in a large clinical trial there was no evidence of clinically relevant interactionin patients receiving other commonly prescribed drugs (e.g. benzodiazepines; barbiturates; NSAIDs such as diclofenac sodium and ibuprofen; paracetamol; frusemide; omeprazole).

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 indicated.

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. The mechanism of this interaction is unknown.

There is limited clinical experience to date on the use of letrozole in combination with 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 letrozole with these drugs does not result in clinically significant drug interactions.

4.6. Fertility, pregnancy and lactation

Effects on fertility

In rats treated with letrozole beginning on day 7 post partum for 9 weeks, mating and fertility were decreased at all doses (0.003-0.3 mg/kg/day; below and similar to the human exposure at 2.5 mg/day). The treated rats also displayed delayed sexual maturation, prolonged diestrus and histological changes of reproductive organs (see section 5.3).

Chronic studies indicated stromal hyperplasia of the ovaries and uterine atrophy in rats administered oral doses equal to or greater than 0.3 mg/kg/day (approximately equivalent to human exposure at 2.5 mg/day, based on AUC). In addition, ovarian follicular atrophy and uterine atrophy were observed in chronic studies of female dogs administered doses equal to or greater than 0.03 and 0.3 mg/kg/day respectively (less than and approximately equivalent to human exposure at 2.5 mg/day).

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.

Use in Pregnancy (Category D)

Treatment of pregnant rats with letrozole at oral doses of 0.03 mg/kg/day during organogenesis was associated with a slight increase in the incidence of fetal malformation among the animals treated. 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. At doses of 0.003 mg/kg and above, higher incidences of resorptions and dead fetuses were also reported. These effects are consistent with the disruption of oestrogen-dependent events during pregnancy and are not unexpected with a drug of this class. No peri/postnatal studies have been conducted in animals.

Letrozole is contraindicated during pregnancy (see section 4.3). Isolated cases of birth defects (labial fusion, ambiguous genitalia) have been reported in pregnant women exposed to letrozole.

Women of child-bearing potential and contraceptive measures, if applicable:

There have been post-marketing reports of spontaneous abortions and congenital anomalies in infants of mothers who have taken letrozole. 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.

Use in Lactation

Letrozole is contraindicated during lactation. It is not known if letrozole is excreted in human or animal milk (see section 4.3).

4.7. Effects on 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.

4.8. Undesirable effects:

Letrozole was generally well tolerated across all studies as first-line and second-line treatment for advanced breast cancer, as adjuvant treatment of early breast cancer, and as extended adjuvant treatment of early breast cancer in women who have received prior standard tamoxifen therapy. Approximately one third of the patients treated with letrozole in the metastatic setting, and approximately 80% of the patients in the adjuvant setting (both letrozole and tamoxifen arms, at a median treatment duration of 60 months), and extended adjuvant setting (both letrozole and placebo arms, at a median treatment duration of 60 months for letrozole) can be expected to experience adverse reactions. Generally, the observed adverse reactions are mainly mild or moderate in nature, and many 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 either the normal pharmacological consequences of oestrogen deprivation (e.g. hot flushes, alopecia and vaginal bleeding).

The following adverse events, not reported in the advanced or clinical trials, were noted in the extended adjuvant setting: arthralgia/arthritis, osteoporosis and bone fractures (see section 5.1- Extended adjuvant treatment of early breast cancer).

The following adverse drug reactions, listed in Table 1, were reported from clinical studies 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 and malignant (including cysts and polyps)	

Uncommon:	Tumour pain (1).
Blood and the lymphatic system disorders	
Uncommon:	Leucopenia.
Immune system disorders	
Very rare:	Anaphylactic reaction.
Metabolism and nutrition disorders	
Very common:	Hypercholesterolaemia.
Common:	Anorexia, appetite increase.
Psychiatric disorders	
Common:	Depression.
Uncommon:	Anxiety (including nervousness), irritability.
Nervous system disorders	
Common:	Headache, dizziness, vertigo.
Uncommon:	Somnolence, insomnia, memory impairment, dysaesthesia (including paraesthesia, hypoaesthesia), taste disturbance, cerebrovascular accident,carpal tunnel syndrome.
Eye disorders	
Uncommon	Cataract, eye irritation, blurred vision.
Cardiac disorders	
Common	Palpitations
Uncommon:	Tachycardia, ischemic cardiac events (2, 3) (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:	Increased sweating.
Common:	Alopecia, dry skin, rash (including erythematous, maculopapular, psoriaformand vesicular rash).
Uncommon:	Pruritus, urticaria.
Very rare:	Angioedema, toxic epidermal necrolysis, erythema multiforme.
Musculoskeletal, connective tissue and bone disorders	
Very common:	Arthralgia.

Common:	Myalgia, bone pain, osteoporosis, bone fractures, arthritis, back pain
Not known:	Trigger finger.
Renal and urinary disorders	
Uncommon	Increased urinary frequency.
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 aesthenia and malaise).
Common:	Peripheral oedema, chest pain
Uncommon:	General oedema, pyrexia, mucosal dryness, thirst.
Investigations	
Common:	Weight increase.
Uncommon:	Weight loss
Injury, poisoning and procedural complication	
Common (4)	Fall (5)

(1) Adverse drug reactions reported only in the metastatic setting.
(2) In the adjuvant setting, irrespective of causality, the following adverse events occurred in the letrozole and tamoxifen groups respectively: thromboembolic events (2.1% vs. 3.6%), angina pectoris (1.1% vs. 1.0%), myocardial infarction (1.0% vs. 0.5%) and cardiac failure (0.8% vs., 0.5%).
(3) In the extended adjuvant setting, at a median treatment duration of 60 months for letrozole and 37 months for placebo, the following AEs were reported for letrozole and placebo (excluding all switches to letrozole) respectively: new or worsening angina (1.4% vs. 1.0%); angina requiring surgery (0.8% vs. 0.6%); myocardial infarction (1.0% vs. 0.7%); thromboembolic event (0.9% vs. 0.3%); stroke/TIA (1.5% vs. 0.8%).
(4) Frequency determined based on FACE study data
(5) In some cases fall was reported as a consequence of other adverse events such as dizziness and vertigo

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions viathe local reporting system.

4.9. Overdose:

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

5. PHARMACOLOGICAL PROPERTIES:

5.1. Pharmacodynamic properties:

Pharmacotherapeutic group

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

Pharmacodynamics

The elimination of oestrogen-mediated stimulatory effects is a prerequisite for tumour response in cases where the growth of tumour tissue depends on the presence of oestrogens. In postmenopausal women, oestrogens are mainly derived from the action of the aromatase enzyme, which converts adrenal androgens - primarily androstenedione and testosterone - to oestrone (E1) and oestradiol (E2). The suppression of oestrogen 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. Data suggest it inhibits the aromatase enzyme by competitively binding to the haem of the cytochrome P450 subunit of the enzyme, resulting in a reduction of oestrogen biosynthesis in all tissues.

In healthy postmenopausal women, single doses of 0.1, 0.5 and 2.5 mg letrozole suppressed serum oestrone and oestradiol by 75-78% and 78% from baseline, respectively. Maximum suppression was achieved in 48-78 h.

In postmenopausal patients with advanced breast cancer, daily doses of 0.1 to 5 mg letrozole suppressed plasma concentrations of oestradiol, oestrone, and oestrone sulphate by 75 - 95% from baseline in all patients treated. With doses of 0.5 mg and higher, many values of oestrone and oestrone sulphate were 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 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, ACTH or in plasma renin activity among postmenopausal patients treated with a daily dose of 0.1 to 5 mg letrozole. The ACTH stimulation test performed after 6 and 12 weeks of treatment with daily doses of 0.1, 0.25, 0.5, 1, 2.5 and 5 mg letrozole 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, 0.5 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 were not affected by letrozole in patients, nor was thyroid function as evaluated by TSH, T4 and T3 uptake.

5.2. Pharmacokinetic properties:

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 mealtimes.

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 14C-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.

Metabolism and elimination:

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 14C-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.

The apparent terminal elimination half-life in plasma is about 2 days. After daily administration of 2.5 mg letrozole, 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.

Effect of age or impaired renal/ hepatic function on pharmacokinetics:

In the study populations (adults ranging in age from 35 to >80 years), no change in pharmacokinetic parameters was observed with increasing age. In a study involving volunteers with varying degrees of renal function (24 hour creatinine clearance 9-116 mL/min) no effect on the pharmacokinetics of letrozole was found after a single dose of 2.5

mg. 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 cirrhosis (Child-Pugh score C) to those in healthy subjects (N=8), AUC and $t_{1/2}$ increased on average by 95 and 187%, respectively, although uncertainty exists about the exact figures because of the wide confidence intervals in the study. Breast cancer patients with this type of severe hepatic impairment are thus expected to be exposed to higher levels of letrozole than patientswithout severe hepatic dysfunction. The available data do not allow any conclusions to be drawn about patients with predominant hepatocellular damage, for example, those with hepatitis C. If the opinion of the treating doctor is that the risk is acceptable, a patient with severe hepatic impairment may be treated without dose reduction, but close monitoring of possible adverse drug reactions is recommended. In addition, in two well-controlled studies involving 359 patients with advanced breast cancer, no effect of renal impairment (calculated creatinine clearance: 20-50 mL/min) or hepatic dysfunction was found on the letrozole concentration.

CLINICAL TRIALS

Adjuvant treatment of early breast cancer

Study BIG 1-98

BIG 1-98, a multi-centre, double-blind, randomised study was conducted in over 8000 postmenopausal women with resected receptor-positive early breast cancer. In this study, patients were randomly assigned 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

This study was designed to investigate two primary questions: whether letrozole for 5 years was superior to tamoxifen for 5 years (Primary Core Analysis and Monotherapy Arms Analysis and whether switching endocrine treatments at 2 years was superior to continuing the same agent for a total of 5 years (Sequential Treatments Analysis).

The protocol specified efficacy endpoints were disease free survival (DFS), overall survival (OS) and systemic disease-free survival (SDFS). The protocol specified primary efficacy endpoint of DFS was defined as the interval between date of randomisation and earliest confirmed invasive loco-regional recurrence, distant metastasis, invasive contralateral breast cancer, second invasive (non-breast) primary cancer, or death from any cause without a prior cancer event. The protocol specified secondary efficacy endpoint of OS was defined as the interval from randomisation to death from any cause. The protocol specified secondary efficacy endpoint of SDFS was defined as the interval from randomisation to

systemic relapse, distant metastasis, appearance of a second (non-breast) primary cancer, or death from any cause, whichever occurred first (i.e. excluding loco regional recurrences in the ipsilateral or contralateral breast). In addition, secondary efficacy endpoints specified in the statistical analysis plan prior to the end of enrollment and prior to an interim analysis included time to distant metastases and time to invasive contralateral breast cancer.

Efficacy results at a median follow-up of 26 months:

Data in Table 2 reflects results of the Primary Core Analysis (PCA) including data from non-switching arms (arms A and B) together with data truncated 30 days after the switch in the two switching arms (arms C and D). This analysis was conducted at a median treatment duration of 24 months and a median follow-up of 26 months. Letrozole for 5 years was superior to tamoxifen for efficacy endpoints of disease free survival (protocol specified), time to distant metastases, and systemic disease free survival, but not for the efficacy endpoints of overall survival and invasive contralateral breast cancer.

Table 2 Disease-free and overall survival (PCA ITT population) at a median follow-up of 26 months

	Letrozole N=4003	**Tamoxifen N=4007**	**Hazard ratio (95% CI)**	***P-Value*[1]**
Disease-free survival(primary) - events (protocol definition, total)	351	428	0.81 (0.70, 0.93)	0.0030
Time to distant metastases (secondary)	184	249	0.73 (0.60, 0.88)	0.0012
Overall survival(secondary) – number of deaths (total)	166	192	0.86 (0.70, 1.06)	0.1546
Systemic disease-freesurvival SDFS (secondary)	323	383	0.83 (0.72, 0.97)	0.0172
Contralateral breast disease (invasive) secondary)	19	31	0.61 (0.35, 1.08)	0.0910

CI = confidence interval, DDFS: time from randomisation to the earliest occurrence of a distant metastasis, SDFS: time from randomisation to systemic relapse, metastasis, appearance of a second (non-breast) primarycancer, or death form any cause, whichever occurred first

[1] Logrank test, stratified by randomisation option and use of prior adjuvant chemotherapy

MAA efficacy results at a median follow-up of 73 months:

The Monotherapy Arms Analysis (MAA) which include data for the monotherapy armsonly provides the clinically appropriate long-term update of the efficacy of letrozole

monotherapy compared to tamoxifen monotherapy (Table 4). In 2005, based on the PCA data presented in Table 3 and on recommendations by the independent Data Monitoring Committee, the tamoxifen monotherapy arms were unblinded and patients were allowed to cross over to letrozole. 26 % of patients randomized to tamoxifen elected to cross over to letrozole – including a very small number of patients who crossed over to other aromatase

inhibitors. To explore the impact of this selective crossover, analyses censoring DFS and OS follow-up times at the date of the selective crossover (in the tamoxifen arm) were conducted, and these analyses as well as the ITT analyses for selective endpoints disregarding selective crossover from tamoxifen to letrozole are summarised for the MAA (Table 3).

At a median follow-up of 73 months and a median treatment duration of 60 months, the risk of a DFS event was significantly reduced with letrozole compared with tamoxifen (MAA ITT analysis: HR 0.88; 95% CI 0.78, 0.99; *P*=0.03; confirming the 2005 PCA results. Analysis of DFS taking account of the selective crossover shows similar benefit (HR 0.85; 95% CI 0.75, 0.96). Similarly, the updated analysis confirmed the superiority of letrozole in reducing the risk of distant disease free survival events (HR 0.87, 0.76, 1.00) as well as the risk of reducing distant metastases (HR 0.85; 95% CI 0.72, 1.00). Additionally, overall survival trended towards significance in the ITT analysis. Analysis of overall survival taking account of the selective crossover shows a significantly greater benefit (HR 0.82 0.70, 0.96) in favour of letrozole.

Table 3 Disease-free and overall survival (MAA ITT population) at a median followup of 73 months

	Letrozole N=2463	**Tamoxifen N=2459**	**Hazard Ratio (95 % CI)**	***P-Value*[1]**
Disease-free survival (primary) - events (protocol definition,total)	509	565	0.88 (0.78, 0.99)	0.03
Time to distant metastases (secondary)	257	298	0.85 (0.72, 1.00)	0.045
Distant disease-free survival (metastases) (secondary)	385	432	0.87 (0.76, 1.00)	0.049
Overall survival (secondary) - number of deaths (total)	303	343	0.87 (0.75, 1.02)	0.08
Systemic disease-free survival (secondary)	465	512	0.89 (0.79, 1.01)	0.065
Contralateral breast cancer(invasive) (secondary)	34	44	0.76 (0.49, 1.19)	0.2
Censored analysis of DFS [2]	509	543	0.85 (0.75, 0.96)	-
Censored analysis of Overallsurvival [2]	303	338	0.82 (0.70, 0.96)	-

CI = confidence interval,
[1] Logrank test, stratified by randomisation option and use of prior adjuvant chemotherapy
[2] Analysis censoring observation times at date of selective crossover if crossover occurred

Sequential Treatments Analyses:

The Sequential Treatments Analysis (STA) addresses the second primary question of the study. The primary analysis for the STA was from switch (or equivalent time-point in

monotherapy groups) + 30 days (STA-S) with a two-sided test applied to each pair-wise comparison at the 2.5% level. These analyses were conducted at a median follow-up of 43 months after switch. Additional, exploratory analyses were conducted from randomisation (STA-R) at a median follow up of 67 months, with the results for each comparison summarised by hazard ratios and 99% confidence intervals.

At a median follow up of 43 months after switch, there were no significant differences in any endpoint from switch in the Sequential Treatments Analysis with respect to either monotherapy (e.g. [Tamoxifen 2 years followed by] letrozole 3 years versus tamoxifen beyond 2 years, DFS HR 0.85; 97.5% CI 0.67, 1.09 and [letrozole 2 years followed by]
tamoxifen 3 years versus letrozole beyond 2 years, DFS HR 0.92; 97.5% CI 0.71, 1.17). At a median follow up of 67 months from randomisation, there were no significant differences in any endpoint from randomisation in the Sequential Treatments Analysis (e.g. tamoxifen 2 years followed by letrozole 3 years versus letrozole 5 years, DFS HR 1.05; 99% CI 0.84, 1.32; letrozole 2 years followed by tamoxifen 3 years versus letrozole 5 years, DFS HR 0.96; 99% CI 0.76, 1.21). There was no evidence that a sequence of letrozole and tamoxifen was superior to letrozole alone given for 5 years.

Safety data at a median treatment duration of 60 months derived from MAA:

In study BIG-98 at a median treatment duration of 60 months, the side effects seen were consistent with the safety profile of the drug. Certain adverse reactions were prospectively specified for analysis, based on the known pharmacologic properties and side effect profiles of the two drugs.

Adverse events were analyzed irrespective of drug relationship. Most adverse events reported (approximately 75% of patients reporting 1 or more AE) were Grade 1 and Grade 2 applying the CTC criteria Version 2.0/ CTCAE, version 3.0. When considering all grades during study treatment, a statistically significantly higher incidence of events was seen for letrozole compared to tamoxifen regarding hypercholesterolemia (52% vs. 29%), fractures (10.1% vs. 7.1%), myocardial infarctions (1.0% vs. 0.5%), osteoporosis (5.1% vs. 2.7%)
and arthralgia (25.2% vs. 20.4%), vulvovaginal dryness (3.6% vs. 1.7%).

A statistically significantly higher incidence was seen for tamoxifen compared to letrozole regarding hot flushes (38% vs. 33%), night sweating (17% vs. 15%), vaginal bleeding (13%
vs. 5.2%), constipation (2.9% vs. 2.0%), thromboembolic events (3.6% vs. 2.1%), endometrial hyperplasia/cancer (2.3% vs. 0.2%), and endometrial proliferation disorders (3.5% vs. 0.6%).

Adjuvant Therapy in Early Breast Cancer, Study D2407:

Study D2407 is a phase III, open-label, randomised, multicentre study designed to compare the effects of adjuvant treatment with letrozole to tamoxifen on bone mineral density (BMD), bone markers and fasting serum lipid profiles. A total of 262 postmenopausal women with hormone sensitive resected primary breast cancer were randomly assigned to

either letrozole 2.5 mg daily for 5 years or tamoxifen 20 mg daily for 2 years followed by 3 years of letrozole 2.5 mg daily.

The primary objective was to compare the effects on lumbar spine (L2-L4) BMD of letrozole versus tamoxifen, evaluated as percent change from baseline lumbar spine BMD at 2 years.

At 24 months, the lumbar spine (L2-L4) BMD showed a median decrease of 4.1% in the letrozole arm compared to a median increase of 0.3% in the tamoxifen arm (difference = 4.4%). At 2 years, overall the median difference in lumbar spine BMD change between letrozole and tamoxifen was statistically significant in favour of tamoxifen (P<0.0001). The current data indicates that no patient with a normal BMD at baseline became osteoporotic at year 2 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 BMD. The differences, however, were less pronounced. At 2 years, a significant difference in favour of tamoxifen was observed in the overall BMD safety population and all stratification categories (P<0.0001). During the 2 year period, fractures were reported by 20 patients (15%) in the letrozole arm, and 22 patients (17%) in the tamoxifen arm.

In the tamoxifen arm, the median total cholesterol levels decreased by 16% after 6 months compared to baseline; a similar decrease was also observed at subsequent visits up to 24 months. In the letrozole arm, the median total cholesterol levels were relatively stable over time, with no significant increase at a single visit. The differences between the 2 arms were statistically significant in favour of tamoxifen at each time point (P<0.0001).

Extended adjuvant treatment of early breast cancer:

A multi-centre, double-blind, randomised, placebo-controlled study (CFEM345G MA-17) was conducted in over 5100 postmenopausal patients with receptor-positive or unknown primary breast cancer. In this study, patients who had remained disease-free after completion of adjuvant treatment with tamoxifen (4.5 to 6 years) were randomly assigned either letrozole or placebo.

The planned duration of treatment for patients in the study was 5 years but the trial was unblinded early because of an interim analysis showing a favourable letrozole effect. At the time of unblinding, women had been followed for a median of 28 months (25% of the patients had been followed-up for up to 38 months). The primary analysis showed that letrozole significantly reduced the risk of recurrence by 42% compared with placebo (hazard ratio 0.58; P=0.00003). The statistically significant benefit in disease free survival (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 independent Data and Safety Monitoring Committee (DSMC) recommended that women who were disease-free in the placebo arm be allowed to switch to letrozole for up to

5 years, when the study was unblinded in 2003. The study protocol was duly amended, implementing the DSMC recommendation: 60% of the eligible patients in the placebo arm opted to switch to letrozole, while the remaining patients opted to have no further treatment but agreed to continue to be monitored. The selective switch to letrozole severely compromised further comparative analyses of efficacy and safety – in the final, close-out analysis after a median treatment duration of 5 years for letrozole, 64% of the randomised placebo arm total follow-up patient-years was actually accrued under letrozole, not placebo.

In the updated, final analysis conducted in 2008, 1551 women opted to switch from placebo to letrozole, at a median 31 months after completion of adjuvant tamoxifen therapy. Median duration of letrozole after switch was 40 months.

All significance levels in the 2008 analysis are provided for information purposes only, not for inference. No adjustment has been made for multiple updates or for multiple endpoints. Analyses of efficacy endpoints "ignoring the switch" compare the randomised letrozole arm with a control arm in which follow-up was approximately one third placebo, two-thirds letrozole. Median treatment duration for letrozole was 60 months; in the placebo arm, median duration of placebo until switch (if a switch occurred) was 37 months.

The updated final analysis, conducted at a median follow-up of 62 months, confirmed the significant reduction in the risk of breast cancer recurrence with letrozole compared with placebo, despite 60% of women in the placebo arm switching to letrozole after the study was unblinded. The protocol-specified 4-year DFS rate was identical in the letrozole arm for both the 2004 and 2008 analyses, confirming the stability of the data and robust effectiveness of letrozole long-term. In the placebo arm, the impact of the selective switch to letrozole is seen in the increase in 4-year DFS rate and in the apparent dilution intreatment difference.

In the original analysis, for the secondary endpoint overall survival (OS) a total 113 deaths were reported (51 letrozole, 62 placebo). Overall, there was no significant difference between treatments in OS (hazard ratio 0.82; *P*=0.29). In node positive disease, letrozole significantly reduced the risk of all-cause mortality by approximately 40% (hazard ratio 0.61; *P*=0.035), whereas no significant difference was seen in patients with node negative disease patients (hazard ratio 1.36; *P*=0.385), in patients with prior chemotherapy, or in patients with no prior chemotherapy. Tables 4 and 5 summarise the results.

Table 4 Disease-free and overall survival (Modified ITT population)

	2004 analysis – median follow-up 28 months			**2008 final update analysis[1] – median follow-up 62 months**		
	Letrozole N=2582	**Placebo N=2586**	**HR (95% CI)[2] *P value***	**Letrozole N=2582**	**Placebo N=2586**	**HR (95% CI)[2] *P value***
Disease-free survival (protocol definition)[3]						
Events	92 (3.6%)	155 (6.0%)	0.58 (0.45, 0.76)	209 (8.1%)	286 (11.1%)	0.75 (0.63,

			0.00003			0.89) 0.001
4-year DFS rate	94.4%	89.8%		94.4%	91.4%	
Disease-free survival including deaths from any cause						
Events	122 (4.7%)	193 (7.5%)	0.62 (0.49, 0.78) 0.00003	344 (13.3%)	402 (15.5%)	0.89 (0.77, 1.03) 0.120
5-year DFS rate	90.5%	80.8%		88.8%	86.7%	
Distant metastases						
Events	57 (2.2%)	93 (3.6%)	0.61 (0.44, 0.84) 0.003	142 (5.5%)	169 (6.5%)	0.88 (0.70, 1.10) 0.246
Overall survival						
Deaths	51 (2.0%)	62 (2.4%)	0.82 (0.56, 1.19) 0.291	236 (9.1%)	232 (9.0%)	1.13 (0.95, 1.36) 0.175
Contralateral breast cancer						
Invasive (total)	15 (0.6%)	25 (1.0%)	0.60 (0.31, 1.14) 0.117	33 (1.3%)	51 (2.0%)	0.64[4] (0.41, 1.00) 0.049

HR = Hazards ratio; CI = Confidence Interval

1. When the study was unblinded in 2003, 1551 patients in the randomised placebo arm (60% of those eligible to switch – i.e. who were disease-free) switched to letrozole at a median 31 months after randomisation. The analyses presented here ignore the switching under the ITT principle.
2. Stratified by receptor status, nodal status and prior adjuvant chemotherapy.
3. Protocol definition of disease-free survival events: loco-regional recurrence, distant metastasis or contralateral breast cancer.
4. Odds ratio and 95% CI for the odds ratio.

Table 5 Disease-free and overall survival by receptor status, nodal status and previous chemotherapy (Modified ITT population)

	2004 analysis – median follow-up 28 months		**2008 analysis – median follow-up 62 months[1]**	
	HR (95% CI)[2]	***P* value**	**HR (95% CI)[2]**	***P* value**
Disease-free survival (protocol definition)				

Receptor status positive	0.57 (0.44, 0.75)	0.000 03	0.74 (0.62, 0.89)	0.001
Nodal status Negative	0.48 (0.30, 0.78)	0.002	0.67 (0.49, 0.93)	0.015
Positive	0.61 (0.44, 0.83)	0.002	0.78 (0.62, 0.97)	0.027

Chemotherapy None	0.58 (0.40, 0.84)	0.003	0.71 (0.54, 0.92)	0.010
Received	0.59 (0.41, 0.84)	0.003	0.79 (0.62, 1.01)	0.055
Overall survival				
Nodal status Negative	1.36 (0.68, 2.71)	0.385	1.34 (0.99, 1.81)	0.058
Positive	0.61 (0.38, 0.97)	0.035	0.96 (0.75, 1.21)	0.710

HR = Hazards ratio; CI = Confidence Interval

1. Including 60% of eligible patients who switched from placebo to letrozole after the study was unblinded in 2003
2. From Cox regression models

In the updated analysis, as shown in Table 4, there was a significant reduction in the odds of an invasive contralateral breast cancer with letrozole compared with placebo, despite 60% of the patients in the placebo arm having switched to letrozole. There was no significant difference in overall survival.

There was no difference in safety and efficacy between patients aged <65 versus ≥65 years.

The updated safety profile of letrozole did not reveal any new adverse event and was entirely consistent with the profile reported in 2004.

The following adverse events irrespective of causality were reported statistically significantly more often with letrozole (n=2567) than with patients who elected not to switch to letrozole after the study was unblinded (n=1026) – hot flushes (letrozole, 60.9% versus placebo, 51.4%), arthralgia/arthritis (41.5% versus 27.2%), sweating (34.8% versus
29.7%), hypercholesterolemia (23.6% versus 15.3%) and myalgia (17.7% versus 9.4%). Most of these adverse events were observed during the first year of treatment.

For patients who elected to switch to letrozole after the study was unblinded, the pattern of general adverse events reported was similar to the pattern during the first two years of treatment in the double-blind study.

Cardiovascular, skeletal and endometrial events were collected with dates of onset and it is possible to report according to the treatment received.

With respect to cardiovascular events, statistically significantly more patients reported overall cardiovascular events with letrozole (9.8%) than with placebo (7.0%). Overall cardiovascular events were reported for 6.2% of the patients who elected to switch to letrozole. Significantly more patients reported stroke/TIA with letrozole (1.5%) than with placebo (0.8%) (letrozole after switch, 0.7%); cardiac events (letrozole, 2.1% versus placebo, 1.0%) (letrozole after switch, 1.4%); and thromboembolic events (letrozole, 0.9% versus placebo, 0.3%) (letrozole after switch, 0.6%).

Fractures were reported significantly more often with letrozole (10.4%) than with placebo (5.8%) (letrozole after switch, 7.7%) as was new osteoporosis (letrozole, 12.2% versus placebo, 6.4%) (letrozole after switch, 5.4%). Irrespective of treatment, patients aged 65

years or older at enrollment experienced more bone fractures and more (new) osteoporosis than younger women.

Updated results (median duration of follow-up was 61 months) from the bone sub-study demonstrated that at 2 years, compared to baseline, patients receiving letrozole had a median decrease of 3.8% in hip bone mineral density (BMD) compared to 2.0% in the placebo group (*P*=0.02). There was no significant difference between treatments in terms of changes in lumbar spine BMD at any time.

Updated results (median follow-up was 62 months) from the lipid sub-study showed no significant difference between the letrozole and placebo groups at any time in total cholesterol or in any lipid fraction. In the updated analysis the incidence of cardiovascular events (including cerebrovascular and thromboembolic events) during treatment with letrozole versus placebo until switch was 9.8% vs. 7.0%, a statistically significant difference.

First-line treatment of advanced breast cancer:

One well-controlled double-blind trial (Study 025) was conducted comparing letrozole 2.5 mg (n=453) to tamoxifen 20 mg daily (n=454) as first-line therapy in postmenopausal women with locally advanced or metastatic breast cancer. The percentage of patients with hormone receptor positive tumours was 64% in the letrozole group and 67% in the tamoxifen group. Letrozole was superior to tamoxifen in time to progression (primary endpoint) and in overall objective tumour response and time to treatment failure. Time to response and duration of response were the same for both drugs. Specific results are presented in Table 6.

Table 6 Results at a median follow-up of 32 months

Endpoint	**Letrozole 2.5 mg N=453**	**Tamoxifen20 mg N=454**	**Hazard ratio or odds ratio (95%CI)**
Time to progression (TTP) (median)	9.4 months	6.0 months	0.72 (0.62, 0.83)
Overall objective tumour response (CR +PR)	145 (32%)	95 (21%)	1.78 (1.32, 2.40)
Duration of overall objective tumour response	25 months	23 months	0.74 (0.54, 1.01)
Time to response (median)	14 weeks	14 weeks	0.96 (0.74, 1.25)
Time to treatment failure (TTF) (median)	9.0 months	5.7 months	0.73 (0.64, 0.84)

CR = complete response; PR = partial response
TTP hazard ratios comparing the risk of progression are presented - a hazard ratio of less than 1 favours letrozole, greater than 1 favours tamoxifen.
Response odds ratios for objective tumour response are presented - an odds ratio greater than 1 favours letrozole, less than 1 favours tamoxifen

Both time to progression and objective response rate were significantly longer/higher for

letrozole than for tamoxifen irrespective of receptor status (Table 7).

Table 7 Receptor Status

Endpoint and subgroup	Letrozole 2.5 mg	Tamoxifen 20 mg	Hazard ratio orodds ratio (95% CI)
Receptor positive (ER and/or PgR+)	**N=294**	**N=305**	
Time to progression (TTP)(median)	9.4 months	6.0 months	0.69 (0.58, 0.83)
Response	33%	22%	1.78 (1.2, 2.6)
Receptor Unknown & other*	**N=159**	**N=149**	
Time to progression (TPP)(median)	9.2 months	6.0 months	0.77 (0.60, 0.99)
Response	30%	20%	1.79 (1.1, 3.0)

TTP hazard ratios comparing the risk of progression are presented - a hazard ratio of less than 1 favours letrozole, greater than 1 favours tamoxifen.
Response odds ratios for objective tumour response are presented - an odds ratio greater than 1 favours letrozole, less than 1 favours tamoxifen.
* 4 patients in the letrozole arm, and none in the tamoxifen arm had one receptor negative and the other unknown, therefore counted as receptor negative.

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 cross-over was virtually completed by 36 months. The median time to cross-over was 17 months (letrozole to tamoxifen) and 13 months (tamoxifen to letrozole). Letrozole treatment in the first line therapy of advanced breast cancer patients is associated with an early survival advantage over tamoxifen. The median survival was 34 months for letrozole and 30 months for tamoxifen. A significantly greater number of patients werealive on letrozole versus tamoxifen throughout the first 24 months of the study (repeated log rank test), see Table 8.

	Letrozole N=458			Tamoxifen N=458			Logrank
Months	**Alive**	**Deaths**	**Crossed to tamoxifen**	**Alive**	**Deaths**	**Crossed to letrozole**	**P-value**
6	426	31	51	406	52	74	0.0167
12	378	79	129	343	114	145	0.0038
18	341	115	185	297	159	179	0.0010
24	286	166	208	263	193	198	0.0246
30	241	209	225	227	227	217	0.0826
36	156	243	233	169	251	224	0.2237
42	70	267	238	85	266	226	0.4820

48	24	277		27	272	228	0.6413
54	6	277		6	276		*0.5303

* Overall Logrank test *P*-value

In patients who did not cross-over to the opposite treatment arm, median survival was 35 months with letrozole (N=219, 95% CI 29 to 43 months) vs. 20 months with tamoxifen (N=229, 95% CI 16 to 26 months).

The total duration of endocrine therapy (time to chemotherapy) was significantly longer for letrozole (median 16.3 months, 95% CI 15-18 months) than for tamoxifen (median 9.3
months, 95% CI 8 to 12 months) (logrank *P*=0.0047).

Worsening of Karnofsky Performance Score (KPS) by 20 points or more occurred in significantly fewer patients on letrozole (19%) than tamoxifen first-line (25%) (odds ratio 0.69 (0.50-0.94), *P*=0.0208).

Second-line treatment of advanced breast cancer:

In a well-controlled double-blind clinical trial (Study AR/BC2), 551 postmenopausal women with advanced breast cancer who had relapse or disease progression following antioestrogen (e.g. tamoxifen) therapy were randomised to receive oral daily doses of either letrozole 0.5 mg, letrozole 2.5 mg or megestrol acetate 160 mg. Some of the patients had also received previous cytotoxic treatment. Patients were either ER positive or unknown status. Data were collected up to 9 months after the last patient was enrolled in the core trial. This was the cut-off date for the primary analysis of response, time to progression, time to failure and safety. For all patients who were still alive at the end of the core trial, whether still on treatment or not, extension data were collected over an additional 6 months (extension trial). The end of the extension trial was the cut-off date for the primary analysis of survival.

At the end of the core trial, the overall objective tumour response (complete and partial response) rate was greatest in patients treated with letrozole 2.5 mg (23.6%) compared to patients treated with megestrol acetate (16.4%) and letrozole 0.5 mg (12.8%). Comparison of the response rates showed a statistically significant dose-effect in favour of letrozole 2.5 mg (*P*=0.004) with letrozole 2.5 mg also statistically superior to megestrol acetate (*P*=0.04). The median duration of complete and partial response was 18 months for letrozole 0.5 mg and for megestrol acetate but was not reached for letrozole 2.5 mg. The duration of response was statistically significantly longer with letrozole 2.5 mg than with megestrol acetate (*P*=0.01). The median time to treatment failure was longest for patients on letrozole 2.5 mg (155 days) compared to patients on megestrol acetate (118 days) and letrozole 0.5 mg (98 days) (*P*=0.007). The median times to progression were not significantly different. The median times to death (unadjusted analysis) were also not significantly different among the treatment groups in the Kaplan-Meier survival curves with many patients still alive at the last analysis (patients still alive: letrozole 0.5 mg (51.6%), letrozole 2.5 mg (58.1%), megestrol acetate (50.3%)). Letrozole gave significantly fewer severe and life threatening side effects, in particular decreased cardiovascular experiences and pulmonary emboli, than megestrol acetate. Other reported drug related adverse events included headache, hot flushes, allergic rash, nausea, hair thinning and oedema (see section 4.8).

Neoadjuvant treatment of breast cancer:

The safety and efficacy of letrozole has not been demonstrated in the neoadjuvant treatment of breast cancer.

5.3. Preclinical safety data:

Repeat dose toxicity studies of up to 12 months duration were conducted in rats and dogs. No-effect levels were not established for letrozole, but changes observed at the lowest doses used (0.03 mg/kg/day) were related directly to the pharmacological properties of letrozole. Plasma levels of letrozole at the lowest dose in rats and dogs were similar to those expected in post-menopausal women during treatment with letrozole.

At higher doses of letrozole, associated with plasma letrozole concentrations 3 to 100 times greater than those expected in humans, changes were observed in the liver (probably related to the enzyme-inducing properties of letrozole), the pituitary gland, skin, salivary gland, thyroid gland, haematopoietic system, kidneys, adrenal cortex and skeletal system (increased bone fragility). Additional lesions observed at similar doses in studies of longer duration were ocular and cardiac lesions in mice.

In juvenile rats, letrozole treatment beginning on day 7 post partum for 6-12 weeks resulted in skeletal, neuroendocrine and reproductive changes at all doses 0.003-0.3 mg/kg/day; below and similar to the human exposure). Bone growth was decreased in males and increased in females. Bone mineral density (BMD) was decreased in females. Decreased fertility 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 and ovarian cysts. With the exception of bone size and morphological changes in the testes, all effects were at least partially reversible.

Genotoxicity

Letrozole did not show evidence of genotoxicity in *in vitro* assays for gene mutations and *in vitro* and *in vivo* assays for chromosomal damage.

Carcinogenicity

A 104 week carcinogenicity study with oral doses of letrozole at 0.1, 1 or 10 mg/kg/day in rats showed an increased development of ovarian benign gonadal stromal tumours at the highest dose (approximately 400 times human exposure at the maximum recommended clinical dose, based on AUC). Female rats showed a reduced incidence of benign and malignant mammary tumours at all dose levels of letrozole. Female mice treated with oral doses of letrozole at 0.6, 6 or 60 mg/kg/day in a lifetime carcinogenicity study showed an increased incidence of ovarian benign granulosa-theca cell tumours at all dose levels.

6. PHARMACEUTICAL PARTICULARS:

6.1. List of excipients

Lactose
Sodium starch glycolate
Microcrystalline cellulose
Hypromellose
Colloidal anhydrous silica
Magnesium stearate
Opadry (04F52158)
yellowPurified water

6.2. Incompatibilities

Not applicable

6.3. Shelf life

36 months

6.4. Special precautions for storage

Do not store above 30°C.

6.5. Nature and contents of container

Alu-PVC blister pack of 3x10's

6.6. Instructions for use, handling and disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

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